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HOW ACCURATE IS THE FDA'S MONITORING OF SUPPLEMENTS LIKE EPHEDRA?

HEARING

BEFORE THE

COMMITTEE ON GOVERNMENT REFORM

HOUSE OF REPRESENTATIVES

ONE HUNDRED SIXTH CONGRESS

FIRST SESSION

MAY 27, 1999

Serial No. 106–60

Printed for the use of the Committee on Government Reform

Available via the World Wide Web: http://www.house.gov/reform

U.S. GOVERNMENT PRINTING OFFICE
61–435 CC WASHINGTON : 2000

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THURSDAY, MAY 27, 1999

HOUSE OF REPRESENTATIVES,
COMMITTEE ON GOVERNMENT REFORM,
Washington, DC.

The committee met, pursuant to notice, at 1:30 p.m., in room 2154, Rayburn House Office Building, Hon. Dan Burton (chairman of the committee) presiding.

Present: Representatives Burton, Morella, Horn, Waxman, Norton, Cummings, Kucinich, Tierney, Schakowsky.

Staff present: Kevin Binger, staff director; Daniel Moll, deputy staff director; Beth Clay, professional staff member; David Kass, deputy counsel and parliamentarian; Mark Corallo, director of communications; Corinne Zaccagnini, system administrator; Carla Martin, chief clerk; Lisa Smith-Arafune, deputy chief clerk; Phil Schiliro, minority staff director; Phil Barnett, minority chief counsel; Kristin Amerling, Cherri Branson, Sarah Despres, and Michael Yang, minority counsels; Karen Lightfoot and Denise Wilson, minority professional staff members; Ellen Rayner, minority chief clerk; Earley Green, minority staff assistant; and Barbara Wentworth, minority research assistant.

Mr. BURTON. The committee will come to order.

I want to apologize for a lot of Members not being here. We had a rule on the floor that went down just a short time ago, and there is a conference going on with a large number of our members expressing their discontent with some of the things that have happened; and I don't know if you have ever been in a food fight, but those things happen from time to time, and I decided to extract myself from that and come up here to be at the meeting. I don't know what the Democrats are doing, but we have two fine Democrat Representatives here so——

Mr. KUCINICH. We are in a supplement fight.

Mr. BURTON. We are getting ready to go on a break back in our districts.

The Chair sees a quorum and a quorum being present, the Committee on Government Reform will come to order. I ask unanimous consent that all Members' and witnesses' opening statements be included in the record, and without objection, so ordered.

We are here today to continue our dialog with the Food & Drug Administration on their regulation of dietary supplements. Today's hearing will focus on the need for a better system to monitor adverse events with dietary supplements.

The Food & Drug Administration is responsible for tracking adverse events for different products, prescription drugs, over-the-counter drugs, infant formula, dietary supplements, and even veterinary medicines.

So what is an adverse event? Clearly, if someone takes a drug or dietary supplement and dies from it, that is a very serious adverse event. If you take a product and suffer a stroke as a result of a heart attack, that is a serious adverse event. If you take a product and develop a skin rash, that is an adverse event, but not necessarily a serious event.

An adverse event can be one or more of a range of things. Why does the Food & Drug Administration have monitoring systems? These are early warning systems to protect the public if food or a drug unexpectedly starts hurting people. The Food & Drug Administration has the authority to seize products which pose a public health risk, or the FDA can propose regulations to limit the way in which a product is used.

Obviously, it is very important that the FDA has an accurate and effective system. People's lives may depend on it. Companies' reputations are at stake. Sometimes millions or billions of dollars of investments can be affected. So it is very important that the FDA does a good job in this area.

Today, we are going to talk about the adverse events monitoring systems for dietary supplements. We have been looking at this system for a while now, and there appears to be some very serious problems.

I think that the FDA will concede that this system has some shortcomings. The point of today's hearing is not to say that we should not have an early warning system. The point of the hearing is that we need to have an accurate system and that the facts need to be checked and good information needs to be provided to the American people. The FDA uses this monitoring system to develop regulations. If you want to have good regulations, you have to have good information.

Through our review, we have identified six problem areas: causality not established. There is no analysis of possible causal relationships between products and adverse reactions for dietary supplements. The FDA does not followup to make sure that an adverse event is actually caused by a dietary supplement.

Ironically, this is done for veterinary drugs. For instance, if a dog takes a medicine and a dog has a heart attack and dies, the FDA evaluates this report to see if the death was related to the drug or not. Because they followed up on the veterinary reports, the FDA was able to determine that in 1997, of 3,000 adverse event reports to the center for veterinary medicine, only 1 percent were definitely associated with a product, 31 percent were probably associated, 45 percent possibly were associated, 12 percent were definitely not related to the product, and 11 percent lacked adequate information to determine association.

With people and dietary supplements events, the FDA has not done this analysis. They cannot provide this type of information. If the FDA does this for animals, why not for people? On the FDA website, two deaths are attributed to ephedra, 15 to ephedrine, and 12 to ma huang.

I have further information on two such cases. This case states that one death attributed to ephedra was actually attributable to hypothermia, the other is the death of a woman who had been using an ephedra supplement. She died after driving her automobile the wrong way on a one-way street and struck a pole going 90 miles an hour. Her blood alcohol limit was .212, more than twice the legally intoxicated limit in most States. Are these two cases really ephedra deaths?

No. 2, no classification of seriousness of event. The website lists over 2,000 adverse events, but there is no evaluation of whether these are mild events, moderate events, or serious events. The impression the FDA gives, especially in the press, is that all of these events are serious events.

According to information provided to the committee by the FDA, of 600 events received, 60 percent were not serious events. Additionally, it is unclear on the website what actually should be reported as an event.

On the prescription drug reporting site, a detailed explanation is given of what an adverse event is. However, the dietary supplement site is vague and lists an adverse event as an illness or injury associated with the use of dietary supplements.

Are there dual definitions for adverse events? This is a very important issue because the FDA frequently quotes the numbers of adverse events in dietary supplements and uses these numbers as a means of developing policy.

I understand my colleagues on the Science Committee have requested a General Accounting Office evaluation of the FDA's use of this monitoring system in the development of policy regarding ephedra. The report is expected to be released in the coming months, and we look forward to utilizing this report in our investigation.

Three, time lag for Freedom of Information Act requests. If someone outside the FDA wants more information on an adverse event, they have to file a Freedom of Information Act request. This process is so slow that sometimes it takes over a year.

Can you imagine being a manufacturer of a supplement and the FDA's website states that someone died after taking your product, and the FDA will not provide you information about the report for over a year? Think about that. You could go out of business because they erroneously put something on a website about an adverse reaction to a product that you produce and they are wrong, and you can't get that corrected for over a year while your product is on the market. You can bankrupt a business when the FDA is wrong. That can't be correct.

One case recently reported in the press was a manufacturer who had 14 events and one death reported on the FDA website for their product, and the FDA told the manufacturer they were too busy to respond to his concerns. They are still waiting after 11 months for the FDA to provide information on these events.

Another requester has still not received information after 1 year. The industry wants to work with the FDA, but how is the industry supposed to be responsive when the FDA will not give them any information?

Is the FDA's response to the pharmaceutical industry the same on prescription drugs or to manufacturers of infant formula and other food products?

Fourth, timely updates to the FDA website. The current website has not been updated since October 1998. This is over 6 months. If the public is looking to this website for information on adverse events and dietary supplements, they are not well served by a system that is not current, that is out of date.

No. 5, brand and corporate name identification without confirmation. The FDA identifies products and companies on the website. Is it appropriate to do so, especially since they did not determine if the product actually caused the event or whether the product was actually consumed by the patient?

So you list something on the website that has not yet been documented or proven, and you put that company in jeopardy without proper information and proper confirmation.

No. 6, incorrect information not purged. Sometimes the FDA makes mistakes. Companies may find their name or product listed as having caused an adverse event when they do not make a product which contains the ingredients listed.

If the FDA went back and fixed mistakes, there would be no problem, but they don't. The FDA commissioner alluded to this problem in response to questions at our March 25 hearing. They told us that it is a monumental task to have the FDA make any changes to a report, so if they make a mistake, it is a monumental task for them to correct the mistake.

Is it a responsible act to leave misinformation about a company on a government website with a small footnote stating the corrected information? With the increased use of dietary supplements by Americans and with concerns about adulterated products, drug interactions and the need to identify public health concerns, an accurate and effective reporting system for dietary supplements should be a high priority for the Food & Drug Administration.

Now, let's talk about ephedra, as an example. In January, the FDA published its priority list for 1999 activities. Resolving the proposed rule on ephedra was listed at the top of the Center for Food and Applied Nutritionals' list for dietary supplements.

Ephedra has been a very controversial supplement. It has been used for thousands of years in traditional Chinese medicine for asthma. Approximately 15 billion servings of ephedra supplements were used last year in hundreds of products.

The plant version of ephedra is used as a dietary supplement. The synthetic version is used in over-the-counter medicines like Sudafed and Primatine Mist. Sometimes it has been abused.

In the past, there have been a few unscrupulous companies that marketed illicit street drugs containing high doses of ephedrine. We applaud the FDA for stopping these companies. We also applaud the respectable supplement manufacturers who worked with the government to stop this criminal activity.

We will hear today from two mothers whose sons died after taking products containing large amounts of ephedrine. Our sympathies are with them and their families.

Let me make it very clear that no one in Congress has fought harder against drug trafficking than I and many of my colleagues.

We have sponsored legislation to give the death penalty to drug pushers. It is my understanding that these products are now off the market, the ones that we are talking about.

If they are not, the FDA clearly has the authority to seize them. This hearing is about whether the FDA is doing a good job in tracking adverse events; are they giving the public and the medical community reliable information.

On the one hand, if a supplement is causing harm, it should be removed from the marketplace. On the other hand, if the FDA is giving the public erroneous information, then potentially good products that help people could be removed from the market and many companies could be in jeopardy. What we need is good information so the American people can make good decisions, and the Congress as well.

This hearing is not about deciding whether the current proposed rule on ephedra is the correct stand or not. It is about finding effective solutions for the obvious problem of an ineffective system so the FDA can fulfill its mandate of protecting the public. With the passage of the Dietary Supplement Health and Education Act, the onus is on the FDA to determine safety of a product, and if it is not safe to remove it from the marketplace.

Some have said that the FDA would like to use a tragedy caused by a few unscrupulous manufacturers to change how we regulate an entire industry, retract the Dietary Supplement Health and Education Act and regulate dietary supplements as drugs, not foods. I hope that is not the case. That is not the right way to make policy.

We are pleased that Dr. Joseph Levitt, Director of the Center for Food Safety and Applied Nutrition at the Food & Drug Administration will be addressing us on the development of the special nutritional adverse events monitoring system. He will detail how this system functions and how it compares to other monitoring systems within the FDA and other HHS organizations.

I have been told by my staff that Mr. Levitt and staff from the FDA plan on leaving after the first panel is finished. I would request, Doctor, that you stay to hear the other witnesses and be available to answer questions that may arise as a result of the other testimony.

Mr. Levitt, I appreciate that you are here today, but these people represent the public that both you and I serve. I really think if it is at all possible that it is valuable for you to stay and hear what they have to say, especially considering that we have two mothers who have lost their sons to adverse events.

We will hold the record open until June 10 to allow written submissions to the record. I will wait until the second panel comes to the table to introduce them. But before I introduce our first panel, I would like to recognize our ranking minority member, Mr. Waxman, for his opening statement.

[NOTE.—The submissions referred to may be found at the end of the hearing.]

Mr. WAXMAN. Mr. Chairman, today's hearing raises important questions about the regulation of dietary supplements. The Food & Drug Administration [FDA] is supposed to ensure the safety and effectiveness of an enormous range of health products, including

supplements. To do so, it is essential that manufacturers report deaths and other adverse events to the FDA. This is the rule that applies in the case of drugs and medical devices.

But the public will be surprised to learn that manufacturing of dietary supplements are exempt from the most basic public health protection. When Congress enacted the Dietary Supplement Health and Education Act of 1994, we severely limited FDA's authority over supplements. FDA may not approve supplements before they are marketed and FDA is held to the very high threshold of demonstrating a "significant or unreasonable risk of illness or injury before it can remove an unsafe supplement from the market."

This is a higher threshold than FDA has for dealing with foods, drugs, or medical devices. This means it is up to the supplement industry to ensure that the products that they are making are safe. But here, too, we have restricted the FDA.

We require all drug and medical device companies to report any adverse events they learn of which are associated with their products, but not dietary supplement companies. Instead, we rely on them on a wholly voluntary system of reporting.

This system is not adequate to protect public health. There are many unavoidable problems with a voluntary reporting system, not least of which is the possibility that manufacturers become aware of problems with products and choose not to share that information with the FDA.

I am interested in learning from today's witnesses how reliable the current system has been and how the system can be strengthened.

I want to commend the chairman for his balanced approach in putting this hearing together. He has graciously and appropriately agreed to allow three witnesses that we have requested to testify. As a result, we are going to have witnesses here today who can tell both sides of the story, including witnesses who have lost family members because of ephedra products.

I look forward to hearing their stories and to learning from their firsthand experience about the need for a strong monitoring system, especially for dietary supplements that do not have to undergo any premarketing testing for safety.

Let me make a final comment about FDA's regulation of ephedra. Ephedra is practically a molecular twin to methamphetamine, or speed. The DEA already has restricted its availability. And, in response to hundreds of adverse events related to ephedra supplements, including several deaths, the FDA proposed to limit the amount of ephedra permitted in supplement doses and to require labeling to fully inform consumers about their risks.

This seems to me sensible. Despite the industry's claims, there is no ephedra ban. No one is going to burst into your home to take away your ephedra. Instead, the regulation appears to contain minimal, common sense health safeguards.

There is a lot of misinformation about ephedra. That is why I found Dr. Tim Johnson's comments this morning on Good Morning America to be so helpful, and I would like to play his comments for the committee. I think he cuts through a lot of false claims and provides a balanced analysis.

[Video tape played.]

Mr. WAXMAN. I hope that we can approach this issue with the same kind of objectivity that Dr. Johnson displayed in his presentation. I welcome our witnesses, and I look forward to their testimony. I hope that out of this hearing we will get information that will help us do our jobs better.

Thank you, very much, Mr. Chairman.

Mr. BURTON. Did you have an opening comment?

Mr. KUCINICH. Just for a minute.

Mr. BURTON. Let me yield to Congresswoman Morella.

Mrs. MORELLA. I want to thank you for calling for this hearing because I look forward to hearing about the adverse event reporting system. But I was just reminded of the fact that recently I had a group of school students who came in and I took them on the floor of House.

I showed them where the Speaker stands; and during the Q and A one of them said, You have a speaker, but do you have a listener? So I am going to be a listener today, and I hope to learn a great deal. Thank you.

Mr. BURTON. That is refreshing.

Mr. Kucinich.

Mr. KUCINICH. Thank you very much, Mr. Burton. I want to thank you, Mr. Burton, for your continuing efforts to provide a balanced public presentation of the possibilities of alternatives of health care in this country.

I think that all of us appreciate the opportunity to look at not only the challenges which face health care but also the possibilities of new approaches that people might use in order to expand their own health and to improve the quality of their lives.

I support your endeavors in looking at alternative medicine, and I know that the concerns that are expressed today about the use of supplements are concerns that ought to be taken with a great deal of seriousness.

It is my view that while food supplements can provide many useful opportunities for people to have better health, I think we are starting to gather a lot of information that would suggest that some degree of professional supervision may be helpful in order to protect the health of the consumer.

Not every consumer has the kind of background that would enable them to be safe in the consumption of some of these products. On the other hand, I don't think that products ought to be withheld from the market simply because they are not approved by the FDA.

Now, this is a very difficult matter that we face, and I know that the testimony will help to resolve some of it, at least for the moment. So I thank you again, Mr. Chairman. Thank you, Mr. Waxman, for your leadership on this issue.

Mr. BURTON. Do other Members wish to be heard?

Mr. Cummings.

Mr. CUMMINGS. Mr. Chairman, thank you very much. I join with my colleagues in expressing appreciation to you for this hearing.

Whenever I go to the health food stores, the place is packed with people trying to improve their health, trying to deal with health problems, and so this hearing is quite appropriate.

The Food & Drug Administration is the governing body charged with the responsibility of regulating the production, distribution,

and consumption of prescription and over-the-counter drugs. In keeping with its general purpose, it seems only natural that the FDA has an adequate system of monitoring the adverse effects of dietary supplement products that are not FDA regulated, specifically those like ephedra.

The need for a careful examination and assessment of the Food & Drug Administration's AER reporting system, particularly in the way of stimulus-like drugs, like ephedra, is evidenced by not only the 38 deaths and the several hundred voluntarily reported cases of adverse events caused by ephedra or synthesized versions, but also in the history of the Federal action involving ephedra, which dates back as early as 1983.

In addition, after giving consideration to the fact that in 1998 the DEA noted an increased relationship between synthesized ephedra and the street drug methamphetamine, it becomes obvious that the nature of this stimulant is one that necessitates mandatory monitoring and reporting of its adverse effects.

I am interested to hear Mr. Levitt's testimony concerning the AER system and how the FDA seeks to modify the process toward making it a more efficient and effective means of monitoring ephedra and other dietary supplements which might have adverse effects to the public. Thank you very much.

Mr. BURTON. I thank the gentleman.

Are there further Members that want to be heard? If not, Mr. Levitt would you come forward.

[Witness sworn.]

Mr. BURTON. We welcome your opening statement, Mr. Levitt.

STATEMENT OF JOSEPH A. LEVITT, DIRECTOR, CENTER FOR FOOD SAFETY AND APPLIED NUTRITION, FOOD AND DRUG ADMINISTRATION

Mr. LEVITT. Thank you, Mr. Chairman and members of the committee. My name is Joseph A. Levitt. I am Director of the FAA Center for Food Safety and Applied Nutrition, often referred to as CFSAN.

Joining me today at the table is Janice F. Oliver, my Deputy Director in the center, and on my right, Dr. Elizabeth A. Yetley, who is Director of the Office of Special Nutritions within our center and it is their office that we regulate dietary supplements.

I am pleased to be here today to discuss FDA's adverse event reporting systems generally, and specifically CFSAN's adverse event monitoring system, referred to by the initials SN/AEMS, which stands for special nutritionals adverse event monitoring system, and this includes dietary supplements.

Mr. Chairman, if I may respond to your request that you made in your statement about my staying at the hearing, while I had not planned to, at your request I will be glad to with the one request that I be allowed a 2-minute break between panels in order to rearrange my schedule.

Mr. BURTON. That is fine.

Mr. LEVITT. Let me begin by saying that we are here today to focus on FDA's adverse event reporting system for dietary supplements. As Dr. Henney stated when she testified before this committee on March 25, 1999, the intent of the Dietary Supplement

Health and Education Act [DSHEA], was to provide consumers with broad access to dietary supplements while at the same time to assure the safety and proper labeling of those products.

The adverse event monitoring system for dietary supplements is a critical part of FDA's ability to meet the consumer protection provisions of the law. We believe the current system serves as a valuable source of information to signal—and we will be hearing that word a lot today—to signal potential hazards associated with the use of dietary supplements.

However, we agree with what you said, Mr. Chairman, in your opening. We believe there are both enhancements and refinements to the current system that need to occur.

As we move ahead, we want to learn from our experience to date, including our experience with ephedra-containing products, which I know that the committee is particularly interested in. We welcome this opportunity to continue a dialog with the committee on this important issue and how we approach this task.

Mr. Chairman, if I may just divert for one moment with your indulgence, since this is my first time for appearing before your committee as a principal witness, let me just share for a moment some of the overall themes that I have tried to bring to the center in the leadership position that I have been at for a little over a year now.

One thing that people are very curious about when somebody takes a new job, is what does that person really stand for? What values does that person bring to the job? And I have over here a poster on my right which stands in our lobby. It is a little faded because it has been there for a year, but it lays out five major values that I have tried to stress in the year that I have been at CFSAN and which I think are very applicable here today.

No. 1 is public health and safety. We are a public health and safety agency and that needs to be our highest priority. Clearly you are recognizing that, and that is the subject of today's hearing.

No. 2 is respect. I think it is very important that we at FDA and in government as public servants show respect for all of those on the outside that we deal with, be they from industry, health professionals, or consumers; and I think Dr. Henney tried to signal that also in her testimony here earlier this spring.

I also think that it is important that we show respect for the law. I am a lawyer. I think in our case the law provides both tools for us to get our job done as well as boundaries that we must live within. As a lawyer I have particular sensitivity to that.

No. 3 is integrity. In all that we do, what FDA needs to stand for more than anything else is we are a group that is independent and able to provide objective assessments for the public. That is the groundwork on which our credibility is based, and that is paramount.

Four is dedication. I have worked at FDA for over 20 years, and I think if there is probably one word that characterizes our work force more than anything else, it is dedication. We have a hard-working, dedicated staff that does its best on behalf of the public.

Finally, it is not just dedication to anything; it is a dedication to excellence—excellence in science, excellence in regulatory policy, excellence in communication. You spell those out as you can see and it spells out pride.

I have tried to bring a sense and culture of CFSAN pride to all of the work that we do; and I have found that in the first year that I have been there, it has been a very valuable galvanizing force to say this is what we stand for. Thank you.

Moving back to dietary supplements, I would like to summarize my written testimony by highlighting three main points.

First, there are inherent strengths, but also inherent limitations in all spontaneous reporting systems, be they for drugs, biologics devices, or dietary supplements.

The major utility of a surveillance system based on spontaneous reports is to generate signals of potential health problems. These signals warrant and demand further investigation and must be evaluated in the context of other information which may include one or all of the following: controlled clinical trials, scientific literature, market and consumer surveys and product analysis.

There are also significant limitations. The major limitations to consider when assessing spontaneously reported information is underreporting of adverse events, report quality, adverse event recognition or attribution, reporting biases that are inherent and estimation of population exposure.

Notwithstanding these very relevant limitations, postmarketing surveillance based upon spontaneous report data has been a very powerful tool for detecting adverse event signals.

Second, within the FDA the most developed system for adverse event reporting is a system used for prescription drugs. This system, however, has had over three decades to mature and benefits from a number of tools not available to dietary supplements, for example, premarket testing a data base, mandatory reporting by manufacturers, and access to market exposure data, sometimes referred to as denominator data.

Moreover, even in its current state, the agency continues to incorporate enhancements into the prescription drug reporting system and to fine-tune it as necessary. By contrast, the agency's reporting system for dietary supplements was developed only recently in 1993. And so comparatively speaking, it is still in its infancy.

This means we are still in the process of developing the infrastructure, the resource base, and the overall framework of this adverse event monitoring system. We recognize that there are many challenges that we face with the current system and we intend to address each area that will make the system stronger.

The fiscal year 2000 budget request which is now before the Congress includes $2.5 million to enhance the adverse event monitoring system within the foods program. Most of these funds would buttress reporting system for dietary supplements as these products provide the largest share of the center's adverse event reports.

If these funds are provided, we would hire several additional clinical staff to review the adverse event reports, and we would develop a system to integrate adverse event reporting and to modernize it for our entire center programs.

This system would also be compatible with other adverse event systems within the agency. We are also now in the process of assessing our longer-term needs as we develop the budget for 2001.

Third and most importantly, notwithstanding its degree of development, the dietary supplement adverse event monitoring system

is capable of and has surfaced important safety issues for the benefit of the American public. This includes identifying a serious manufacturing product in samples of raw material labeled "plantain" that contained digitalis, and more recently identifying the basis for removing from the market products contain gamma butyrolactone or GBL.

It is critical that FDA be able to move rapidly to protect consumers when significant safety problems arise, and I believe there is general acceptance of that principle.

In closing, Mr. Chairman, I would like to place in context today's subject of adverse event reporting for dietary supplements as it relates to our commitment to develop this calendar year an overall strategy for achieving effective regulation of dietary supplements under the law.

As part of our ongoing consultation with stakeholders, the agency has scheduled two public meetings to solicit comments that will assist CFSAN in developing a strategy and this will include, certainly, input on adverse event reporting for dietary supplements.

The first meeting is coming up soon, July 8 in Washington, DC. The second is on July 20 in Oakland, CA. I will personally chair each of these two meetings. I would encourage interested persons to attend one of these sessions.

It is not necessary to attend both, as we are essentially repeating the same meeting on the West Coast so as to save stakeholders the time and expense of traveling East. For those who cannot attend, comments may be submitted in writing to the public document.

We look forward to input on development of an overall strategy for dietary supplements. Developing the solid blueprint for implementing the DSHEA is essential. This will ensure that the implementation is guided by a framework that will both protect consumers and enable them to make informed choices by using dietary supplements to improve their health.

Thank you, Mr. Chairman. I would be happy to respond to questions you may have. I also note I am getting a note passed to me that I have misspoken. The two public meetings, one is in June. It is on June 8. The second is on July 20. I am sorry if my eyes skipped down.

Thank you very much for your attention. I will be happy, with my colleagues, to try to answer questions.

Mr. BURTON. Thank you, Mr. Levitt, and thank you for that correction.

[The prepared statement of Mr. Levitt follows:]

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

STATEMENT

BY

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

BEFORE THE

COMMITTEE ON GOVERNMENT REFORM

U.S. HOUSE OF REPRESENTATIVES

MAY 27, 1999

FOR RELEASE ONLY UPON DELIVERY

I. Introduction

Mr. Chairman and Members of the Committee, my name is Joseph A. Levitt, Director, Center for Food Safety and Applied Nutrition (CFSAN), Food and Drug Administration (FDA or Agency). I am joined by Janice F. Oliver, Deputy Director, CFSAN and Elizabeth A. Yetley, Ph.D., Director, Office of Special Nutritionals, CFSAN. I am pleased to be here today to discuss FDA's adverse event reporting systems generally, and specifically, CFSAN's Adverse Event Monitoring System called SN/AEMS, which is for special nutritional products, including dietary supplements. In meeting the Agency's mission, one of our responsibilities is to monitor marketed medical products, foods, cosmetics, and dietary supplements for unexpected adverse events. FDA surveillance programs alert the Agency to potential threats to the public health and help Agency experts identify the need for preventive actions.

As Jane E. Henney, M.D., Commissioner of Food and Drugs, stated on March 25, 1999 during a hearing before this Committee, the Dietary Supplement Health and Education Act of 1994 (DSHEA) amended the Federal Food, Drug, and Cosmetic Act to define the term "dietary supplement" and to establish a regulatory framework for dietary supplements. DSHEA provides broad access to dietary supplements for consumers and recognizes that there is a need for a rational regulatory framework that provides FDA authority to remove from the market products that pose a "significant or unreasonable" risk to consumers and that are otherwise adulterated, and to require that labeling for dietary supplements be accurate. The SN/AEMS system is a critical part of FDA's

ability to meet the consumer protection provision of the law. While the current system has served the Agency well thus far, we believe there are enhancements to the SN/AEMS system that certainly should occur. We welcome this opportunity to continue that dialogue with you.

II. Background

Let me begin by providing a brief overview of the adverse event reporting system for drugs, highlighting the purpose and differences of that system compared to the system for special nutritionals, which include dietary supplements. Then, I will specifically discuss the system at CFSAN for monitoring adverse event reports for dietary supplements. For your information, a brief summary of the adverse event reporting systems for all other FDA-regulated products is included in an Appendix to this testimony.

As you know, FDA's responsibilities include postmarketing evaluation, which includes risk surveillance and assessment that rely primarily on two methods of adverse event reporting to the Agency: 1) direct, voluntary reporting by concerned parties, including health professionals and consumers; and, 2) mandated reporting by drug (including biologics) and device manufacturers, distributors, and medical device user facilities. Under the current system, FDA shares this responsibility with manufacturers, healthcare providers, user facilities, patients and consumers. Each participant has a role in monitoring and evaluating adverse events associated with medical products, foods, and

cosmetics. The roles assigned to manufacturers and FDA are defined primarily by statute, while the roles of others are not.

The specific objectives of FDA's postmarketing risk assessment programs are to:

- detect adverse events not previously observed,
- for drugs, biologics, or medical devices; improve understanding of the potential severity of previously anticipated risks, listed on the product's labeling,
- detect adverse events resulting from multiple possible interactions, such as drug interactions or drug-food interactions.

These reporting systems serve as an early warning signal for identifying potential problems.

III. Changes in the Postmarket Surveillance Environment

Changes are occurring in several areas that will affect the Agency's current postmarketing surveillance systems. First, the Prescription Drug User Fee Act and the FDA Modernization Act of 1997 have resulted in some changes in postmarketing reporting requirements. For example, with regard to medical devices, the Modernization Act directs FDA to move away from universal, mandatory adverse event reporting by user facilities to a system based on reporting by a representative sample of facilities.

In addition, shifts in the health care environment and in international marketplaces are affecting the potential for adverse events caused by medical interventions. For example,

with patients now being treated by multiple healthcare providers, a single provider may not have full knowledge of the patient's medical history and use of various medicines and other products. A prescriber's lack of information can lead to increased risk of drug interactions, as one physician may not be aware of what another has prescribed or recommended. The dietary supplement industry has grown dramatically, as has consumption of dietary supplements. Surveys show that more than half of the U.S. adult population uses dietary supplement products. The increasingly global marketplace also could result in a greater potential for rapid, large-scale consumer exposure to new products, which carries a proportional potential for more unexpected adverse events. Finally, the rapid development of new medical interventions for a variety of previously untreatable (or less satisfactorily treatable) conditions results in more individuals using these new interventions. These shifts in the healthcare environment are challenging the existing system and should be considered as we examine FDA's adverse event reporting or monitoring systems.

IV. Adverse Event Reporting Systems

MEDWATCH

While the U.S. has one of the most rigorous premarket approval processes in the world, it is not possible to detect all potential problems during premarketing clinical trials of drugs and medical devices, or premarketing evaluation of the safety of food additives. In addition, not all products that FDA regulates require premarket approval - such as dietary

supplements, conventional foods, and cosmetics. The need for postmarketing surveillance is the direct result of these limitations.

FDA receives spontaneous reports of *suspected* adverse events from manufacturers, user facilities, healthcare professionals, and consumers. Through a program called "MEDWATCH, the FDA Medical Products Reporting Program," healthcare professionals and consumers are encouraged to report serious adverse events and product problems to FDA, the manufacturer, or both. MEDWATCH has established four methods for the public to report to FDA: phone (via a toll-free number), fax (via a toll-free number), direct mail (using a postage paid form), and Internet (via the interactive form on the MEDWATCH website).

MEDWATCH was announced June 3, 1993. While FDA's longstanding postmarketing surveillance programs predate MEDWATCH, this educational initiative was designed to enhance the identification and reporting of adverse events related to the use of FDA-regulated products. Through the MEDWATCH program, health professionals can report serious adverse events and product problems that occur with such medical products as drugs, biologics, medical and radiation-emitting devices, and special nutritional products (i.e., medical foods, dietary supplements and infant formulas). When a health care professional suspects that a product may be related to a serious event, FDA encourages the health professional to submit a MEDWATCH report. Health professionals, however, are welcome to report any adverse event that they judge to be clinically significant.

Adverse Event Reports come into FDA in many ways - either through MEDWATCH, where they are transferred to the appropriate Center; directly to the Center; or through an FDA District or Field Office. Regardless of the path into the Agency, reports are directed to the appropriate Center to be recorded and reviewed.

Strengths and Limitations of Spontaneous Reports Data

For medical devices and drugs (including biologics) adverse event reporting or monitoring systems serve as critical tools to identify potential health hazards that were not anticipated or identified in pre-market safety evaluations. In the absence of premarket review data, the SN/AEMS serves as a critical source for gathering data about the safety of dietary supplements. These systems serve to augment, not replace, other systems and tools for determining the safety of products. Like all passive surveillance systems, however, there are strengths and certain limitations.

The strengths include:

- Generation of Hypotheses and Signals: The great utility of spontaneous report-based surveillance programs is to generate signals of potential public health problems that warrant further investigation. For this reason, adverse event reports must be evaluated in the context of other information, which may include controlled clinical trials, case reports in the scientific literature, the known physiological and pharmacological effects of the substance suspected of being associated with adverse events, market and consumer surveys, and product analysis.

- Clinician Contribution: Health professionals often identify and document adverse events in the clinical settings in which they work. They can provide in-depth information in the adverse event report, thereby providing key input to any postmarketing surveillance system. Thus, while possessing inherent limitations, postmarketing surveillance based on spontaneous report data from clinicians is a particularly powerful tool for detecting adverse event signals of direct clinical impact.

The limitations include:

- Underreporting: Adverse events associated with product use are known to be significantly underreported, since many consumers and health professionals may not recognize a link between the use of a particular product and a subsequent injury or illness, or they do not report the adverse event to appropriate health care agencies. Indeed, because reporting is voluntary (except in the case of certain adverse events that childhood vaccine health care providers, device user facilities, and drug and device manufacturers must report), adverse events which are not reported almost certainly occur.

- Report Quality: Under research protocols, information is collected in a systematic and standardized manner to test a particular hypothesis, and such protocols include numerous quality control procedures to assure reliability and validity of data collected. By contrast, a passive surveillance system is dependent on information contained in voluntary reports from consumers, family, friends, or from health professionals based on patient information and evaluations. FDA attempts to obtain

follow-up data to add to the completeness, clarity, and relevance of a report that associates a clinically serious event with the use of regulated products. Success in obtaining such information, however, is variable. Thus, information received in a passive reporting system is not standardized and often is incomplete. Nonetheless, the reports provide valuable public health information on potential safety problems. Where there is a basis for concern, prudent public health policy leads FDA to take action to protect against unsafe uses of marketed products.

- Adverse Event Recognition: An attribution between the product and the observed event may not be assumed with all spontaneously reported events. This consideration emphasizes the crucial need for careful, thoughtful review of adverse event reports upon their receipt by FDA or the manufacturer and the review of other available scientific information.

- Biases: Unlike clinical trial data, which are obtained under strictly controlled conditions, spontaneously reported information is uncontrolled, and therefore subject to the possible influence of a number of biases that can affect reporting. These biases include the length of time a product has been on the market, country, reporting environment, and quality of the data.

- Estimation of Population Exposure: As a general matter, accumulated case reports cannot be used to calculate incidence rates. Numerator and denominator limitations described above make incidence rates computed from spontaneously reported data

problematic. Compounding these numerator limitations is the lack of denominator data, such as user population and product exposure patterns, that would provide the exact number of consumers exposed to the medical product, and thus at risk for the adverse event of interest. Even if the exposed population is not precisely known, however, estimation of the exposure can be attempted through the use of product utilization data, when it is available for the product. This approach, whose basic methodologies are applicable to medical products in general, can be of great utility. Such utilization data are not available, however, for dietary supplement products, and so making confident estimates of overall exposure in the population is generally not feasible.

FDA Evaluation of Reports of Adverse Events

The very nature of spontaneously reported data places great importance on the evaluation of submitted reports of adverse events. This process is perhaps most accurately characterized as a method, applied on a case-by-case basis, that is based on experience, knowledge of the product being monitored, and awareness of the strengths and limitations of the data.

a. Spontaneous reporting systems – Center for Drug Evaluation and Research

In the case of pharmaceuticals, FDA pays particular attention to all reported serious adverse events that are not in product labeling. Other reports are entered into the database for use in aggregate analysis. In focused evaluation of adverse events, the

postmarketing surveillance database is searched for other reports, and further steps are taken, such as literature searches and use of medical product utilization databases.

Adverse Event Reporting System (AERS)

The Center for Drug Evaluation and Research (CDER) uses a passive, spontaneous reporting system to provide monitoring capability to detect rare and unexpected adverse reactions to marketed drugs. Data are generated primarily as "spontaneous" reports observed and reported by practicing health care practitioners – i.e., reports that originate from observations made in the usual practice of medicine.

FDA began computerizing adverse drug reaction reports (ADRs) in the mid-1960s and legacy data is available dating back to 1969. This computerized system, called the Spontaneous Reporting System (SRS), was replaced by the newer Adverse Event Reporting System (AERS) in November 1997. It is the cornerstone system providing technology for safety monitoring of "spontaneous" data for CDER and the Center for Biologic Evaluation and Research (CBER) therapeutic agents. Currently, adverse drug reactions are reported to FDA in a variety of ways and provide a database of some two million reports that can be analyzed individually or in the aggregate. In FY1998, more than 230,000 reports of suspected adverse events were received by AERS.

Reports of adverse events on marketed human drugs and non-vaccine biologics include prescription drugs (whether or not they are the subject of an approved New Drug Application (NDA)), generic drugs, over-the-counter (OTC) drugs that are the subject of

an approved NDA and non-vaccine biologics. These reports reach FDA through either the drug/biologic manufacturers or direct contact (MEDWATCH). When a health practitioner notifies a manufacturer about a possible reaction, the manufacturer is required by law and regulations to report these observations to FDA.

There are two major sources of OTC drug adverse event reports in FDA:

1) Manufacturers of OTC drugs with NDA's are required by the postmarketing regulation (21 CFR 314.80) to report any serious and unexpected adverse events in 15 days and other type reports periodically as specified by the regulations – the same as for prescription drugs. Given that most of these agents have been on the market for many years and safety of the drugs have been monitored extensively, very rarely are new and rare adverse events identified. More frequently reports are consumers' complaints of lack of expected effect, which is usually a subjective measurement of efficacy (or lack thereof).

2) Voluntary reporting of OTC monographed drugs by consumers or manufacturers is a second source of data. These are greater than 300,000 individual OTC products with more than 700 active ingredients under OTC monographs in place or under development. As expected where these drugs are used appropriately, most adverse events are not serious but in an effort to standardize safety reporting, FDA is considering a proposed regulation mandating reporting of all serious reports, expeditiously, to monitor the rare adverse events and potential product or manufacturing problems.

A minimum data set for a report is currently defined as a report having an identified drug/therapeutic, a definable reaction, a reporter and a patient or subject. For an adverse reaction report to be interpretable, it must contain descriptions of the reaction, the exposure to the drug/therapeutic, the temporal relationship between exposure and reaction, and the underlying disease.

Substantial effort is placed on the review of the case reports for purposes of identifying those with serious outcomes involving adverse event reports not currently in a drug/therapeutic product's labeling. The goal of evaluation of "spontaneous" data is to provide a signal that can be evaluated, quantified and validated as a drug/therapeutic outcome and to ensure appropriate dissemination of risk management information and initiation of regulatory action. Typically, this information may result from as few as several well-documented cases to a very large number of reports that are then evaluated and subjected to signal development. This process involves application of epidemiological methods and includes clinical evaluation of cases for the conditions relating to drug exposure and for the identification of potential risk factors, and confounders of the adverse event report's occurrence. It also includes demographic description and quantification of the exposed population. In the best of circumstances, estimates of reporting rates are possible, using the reported number of adverse event report cases as the numerator and an estimate of prescription drug use as the denominator. At this point in the process, additional data, derived from literature sources, observational or clinical studies, linked databases or other sources of drug usage

data are considered to strengthen or clarify the reported observations for regulatory action.

When a signal of a potential adverse reaction is detected, safety evaluators consult with product reviewers, medical officers, and epidemiologists to review available data and consider further options. Focused studies may be undertaken using various epidemiological and analytical databases and other resources. Based on the results of these studies and evaluations, FDA may decide to disseminate risk information, such as Dear Healthcare Professional letters, and may initiate regulatory action.

Characteristics That Support Drug Spontaneous Reporting

The following characteristics are important in ensuring that the current system is effective in identifying serious, unlabeled events of interest via the spontaneous system for drugs. In general, these are not features of Special Nutritional products reporting:

- Manufacturer Reporting vs. Direct Reporting

Spontaneous reporting of Adverse Event for drugs is heavily driven by Manufacturer Reporting (some 90% of all reports received). Manufacturer reporting (except for OTC monograph drugs) is required by regulation, is well accepted, and leverages the firm's resources in identifying, assessing, and following up on reports of drug injury.

- Quality Assurance

Current good manufacturing practice requirements for all firms manufacturing, labeling, and distributing drugs in the U.S. provides a basis for assuring that the agent identified in the report is the drug in question with the contents meeting the appropriate standards of potency, strength, and purity.

- Drug Label

The Drug Label provides information for the indication and safe and effective use of the product as well as information on the known adverse effects and contraindications.

- Premarket Clearance

Premarket clearance for drugs (except for OTC monograph drugs) provides data for an initial assessment at the point of approval of the benefit – risk assessment and a good starting point for evaluating the agent when it goes beyond the target population after commercialization.

- Benefit-Risk Assessment

The benefit-risk assessment is the continuing process of evaluating the new risks seen postmarketing against the known benefits of the drug. Again, premarket clearance provides a basis for comparison as the safety picture evolves.

- Additional Aspects of Drug Pharmacovigilance

By regulation, serious unlabeled foreign reports are reported to CDER, providing a broader view to the overall benefit – risk picture, sometimes world-wide. In addition, the benefits of 30 years of reporting have resulted in a system that is widely accepted by corporate culture. The Agency also provides regulation, guidance, and compliance oversight to ensure good reporting practices. Finally, evolving regulations reflecting the International Conference on Harmonization (ICH) initiatives and focusing on standardization of requirements have been widely discussed and accepted by industry.

- Learned Intermediary

For prescription drugs, the intervention of a "learned intermediary" (variety of health practitioners) provides a mechanism to supply ongoing individual risk-benefit assessment in the practice of medicine, pharmacy, etc. and to provide a conduit for reporting adverse events.

Let me now address FDA's spontaneous reporting system for dietary supplements.

b. Spontaneous reporting system – for dietary supplements

Special Nutritionals Adverse Event Monitoring System (SN/AEMS)

The SN/AEMS was established in early 1993, following the establishment of the Office of Special Nutritionals. The SN/AEMS system, while formally part of CFSAN's Adverse Reaction Monitoring System, is still in its infancy when compared to the more

formal and well-developed adverse event reporting systems that exist for other products regulated by FDA. It provides, however, an essential monitoring tool for identifying potential serious public health issues that may be associated with the use of a particular product or type of products already in the marketplace that need to be investigated and critically evaluated.

SN/AEMS is limited to those adverse events reported with the use of special nutritional products, which include dietary supplements, infant formulas, and medical foods. The adverse events received on special nutritional products include a variety of both acute and chronic adverse effects. Typically, special nutritional products are used for prolonged periods and often by special or vulnerable populations. Furthermore, dietary supplements often contain multiple substances that may have physiological or even pharmacological effects. The adverse events seen with these products, therefore, tend to require extensive follow-up and evaluation.

Because of these factors, when a serious adverse event is reported in association with a dietary supplement product, considerable resources are expended by FDA to obtain even basic information on the product (e.g., the product name, manufacturer, ingredients, and directions for use). Information is also needed on how the consumer used the product and the nature, severity, patterns, and outcome of the adverse event. Given that reported safety information is limited for most dietary supplement products, SN/AEMS is a critical tool for identifying new or emerging public health problems that may be associated with the use of particular products. Further, the signals generated by

SN/AEMS help focus Agency resources on products needing further investigation. Compared to the CDER adverse event reporting system, the SN/AEMS lacks many of the tools at CDER's disposal – premarket testing database, mandatory reporting by manufacturers, registration of firms and listing of products, good manufacturing practice requirements, and a mature internal database system with which to manage the wealth of information they receive.

These are some of the challenges CFSAN faces with the current system and we are working to address the many areas that will make the system stronger. Specifically, based on the Agency's FY 2000 budget request, CFSAN is developing plans to recruit and train additional appropriate medical staff, and enhance the SN/AEMS system, including integration into an FDA-wide system. A major emphasis will be placed on upgrading and improving the computer infrastructure to facilitate signal and report generation. In addition, as you know, FDA now provides summary information on its special nutritionals AER database on its homepage (www.fda.cfsan.gov). Interested persons may either browse the web report or search for specific ingredients, reports, or types of adverse events. Since its inception, this web site has been very popular. On average it is accessed approximately 3,000 – 4,000 times per month.

We heard the concerns the Committee raised at the March 25 hearing regarding correcting errors to records on the web, and concerns both the Committee and industry have raised about access to those records under the Freedom of Information Act (FOIA). Providing industry access to accurate information in a timely manner, within the

boundaries of the FOIA, and having sufficient resources to apply to maintaining accurate web site records on a real time basis are issues CFSAN is grappling with. We would welcome further discussion with the Committee on these issues.

Like the adverse event reporting system for CDER, the SN/AEM system also receives information from a variety of sources, as identified in Chart A. For dietary supplements, all such reporting is voluntary. As you can see in Chart B, when CFSAN receives a suspected adverse event report on a dietary supplement, it conducts an initial review to determine the seriousness or clinical significance of the report. If the report is considered serious or clinically significant, immediate follow-up information is requested if needed.

The requested follow-up information may include copies of the product(s) label and labeling, information on how the consumer used the product(s), and available medical or other clinical records concerning the reported adverse event. As noted above, the Agency's ability to follow-up has potential limitations based on a variety of factors, e.g., the product sample has often been discarded. After the initial review, CFSAN conducts a medical/clinical review and evaluation to determine whether the report signals a potential public health problem, and if so, what action the Agency should take.

In addition to efforts within FDA to ensure the safe use of dietary supplements, education of the public in an appropriate and timely manner about potential adverse effects associated with these products is critical. In an era of limited resources, the coordinated efforts of Federal agencies, academia, public health groups, industry, and consumers will

be required. As you may recall, when Dr. Henney testified on March 25, she mentioned the Agency's commitment to developing, this calendar year, an overall strategy for achieving effective regulation of dietary supplements under DSHEA. Dr. Henney also stated that in doing so, FDA will provide ample opportunity for public input. As part of this ongoing consultation with FDA's stakeholders, the Agency will hold public meetings on June 8, 1999, in Washington, D.C., and on July 20, 1999, in Oakland, California, to solicit comments that will assist CFSAN in the development of that strategy, including input on the SN/AEM system. Finally, as noted last year in FDA's response to the Report of the Commission on Dietary Supplement Labels, FDA has asked our Foods Advisory Committee (FAC) to play an active role in two important issues: First, to consider how best to gather data on how consumers use information on dietary supplement labels to make decisions as to whether or not a dietary supplement is appropriate for them. FDA asked the FAC to consider the development of guidelines or criteria that could be used by the dietary supplement industry and others to conduct consumer research studies or to evaluate the results of consumer research studies; and, Second, to consider the issue of postmarket surveillance and particularly how best to collect and share surveillance information. The FAC considered these issues at their February 1998 meeting and referred them to FAC working groups to develop recommendations for consideration by the full Committee. The Agency also is considering whether to establish a separate Advisory Committee or Expert Panel devoted to dietary supplement issues, an idea that was also raised at the March 25 hearing.

V. How AER's Benefit Public Health

While there certainly are limitations to passive spontaneous reporting systems, as I have outlined above, I would like to discuss a few examples of how these systems have provided a great benefit to public health.

Adverse Event Reporting System (AERS)

Tasmar

Tasmar (tolcapone) was approved on January 29, 1998, as adjunct therapy (with levodopa and carbidopa) for the treatment of the signs and symptoms of idiopathic Parkinson's disease. The labeling included (in the Precautions Section) a statement on reversible hepatic enzyme abnormalities and recommended monthly monitoring during the first three months of treatment and every six weeks for the following three months. Recommendations also included discontinuing the drug when enzyme elevations equaled or exceeded five times the upper limit of normal, or at the appearance of jaundice. Postmarketing surveillance identified 17 cases of liver-related adverse events following approval including: five hepatitis, three jaundice, and nine other liver function abnormalities. Five pivotal cases were identified with hepatitis documented with increased hepatic transaminase levels and biopsy/radiographic examination suggesting likely drug induced hepatitis related to Tasmar therapy. Two of the five cases reported fatalities from fulminate hepatitis or liver failure from less than three months of therapy-one from Switzerland and one from the U.S. All five pivotal cases experienced hepatitis

within six weeks of therapy that was initially undetected, potentially due to lack of adequate monitoring of liver functions as recommended in the labeling.

In November 1998, FDA asked the sponsor of Tasmar to revise the labeling to include the new warning on hepatotoxicity and a "Dear Doctor" Letter was sent to alert the prescribing physicians and patients with a new requirement of liver function monitoring every two weeks during Tasmar treatment. Since November 1998, FDA has not received any more serious case reports of liver related injuries associated with Tasmar.

Special Nutritionals/Adverse Event Reporting System

Digitalis

In our March 25 testimony, we referenced this case as an example of how the Agency uses a variety of regulatory tools from enforcement actions to rulemaking when it has found dietary supplements that cause safety concerns. This case also is a good example of how AERS serve as our early warning signal and how just one AER can be a powerful indicator of a safety concern.

In 1997, FDA received an AER regarding a young woman with life-threatening abnormal heart function who required hospitalization for six days. FDA immediately conducted an investigation. The Agency detected the botanical Digitalis lanata in samples of raw material labeled "plantain" that was an ingredient in one of the dietary supplement products used by this young woman. Digitalis is a powerful heart stimulant whose

effects may include nausea, vomiting, dizziness, headache, confusion, hypotention (low blood pressure), vision disturbances, and abnormal heart rate and rhythm.

FDA then traced all uses of the contaminated ingredient and asked manufacturers and retailers to recall these products from the market. FDA issued several press releases warning consumers not to purchase or ingest certain dietary supplement products labeled as containing plantain because these products may contain Digitalis lanata, a plant that can cause life-threatening heart reactions, including cardiac arrest, if ingested. While fast and effective actions by FDA prevented further serious adverse effects, which would have likely occurred if these contaminated products remained in the marketplace, it was a single AER that led the Agency to take action.

GBL

Gamma butyrolactone (GBL) is a metabolic precursor to gamma-hydroxybutyrate (GHB), an unapproved new drug and one of the "date rape" drugs. GBL is promoted as a dietary supplement with claims to stimulate growth hormone release, fight stress, increase athletic performance, combat aging, promote sleep, as well as other uses. It is a manufacturing intermediate and industrial solvent. Products containing GBL have been marketed under various brand names, including Renewtrient, Revivarant or Revivarant G, Blue Nitro or Blue Nitro Vitality, GH Revitalizer, Gamma G, Invigorate, and Remforce. GBL has been associated with serious, life-threatening adverse events and the Agency has initiated action to remove it from the marketplace.

FDA had received 55 reports of adverse events by January 13, 1999 (95 AER's as of February 26, 1999), including one death. In 19 of those cases, the consumers became unconscious or comatose and several required intubation for assisted breathing. Other reported effects included seizures, vomiting, slow breathing, and slow heart rate. There were reports of at least five children under 18 years of age who have been injured or who have suffered these kinds of effects.

FDA's analysis of available scientific information, including the opinion of independent outside scientific/medical experts, concluded that GBL's presence in the marketplace represented a serious public health hazard due to its steep dose response curve, ability to induce respiratory arrest and coma, and its serious abuse potential. The Agency concluded that label information, such as warning/caution statements and directions for use, could not provide for its safe use. FDA issued a public warning on January 21, 1999, alerting consumers of the potential hazards from consumption of GBL-containing products.

Firms known to produce or distribute GBL were contacted beginning on January 19, 1999. Warning letters were delivered, beginning on January 27, 1999, to firms not voluntarily recalling their products. The warning letters state that FDA considers GBL to be an unapproved new drug, that these products do not meet the statutory requirement to be marketed as a dietary supplement, and that, even if they could be considered dietary supplements, they do not meet the safety requirements of the law. As of May 20, 1999, FDA has initiated two court-ordered seizures of GBL-containing products.

Ephedra

As you know, on June 4, 1997, FDA published in the *Federal Register* a proposed rule on Dietary Supplements Containing Ephedrine Alkaloids (62 FR 30678). There are a variety of opinions about the proposed rule and the direction the Agency should take. One cannot dispute, however, the shear volume of the reports of illness and injuries that FDA received reported to be associated with the use of dietary supplements suspected to contain ephedrine alkaloids.

Between 1993 and mid-1996, FDA received about 1,600 AER's reported to be associated with the use of dietary supplement products in general. Of these, over half of the AER's were reported to be associated with the use of dietary supplements that contained, or were suspected to contain, ephedrine alkaloids. These adverse events tended to involve cardiovascular system effects and nervous system effects. FDA evaluated these reports and found that the single most common element was that the products contained, or were thought to contain, a source of ephedrine alkaloids (62 FR 30679).

FDA used the information available in the approximately 600 AER's that were in the Agency's possession as of June 7, 1996, to describe patterns associated with these reports. A review of the demographic information showed that in over half of the reported adverse events, the injured party was under 40 years of age. Almost 75 percent of the adverse events were reported to occur in females, often using products promoted for weight loss (62 FR 30683). About 59 percent of the adverse events were reported to occur within 4 weeks of starting to use the product. About 14 percent of the reported

adverse events occurred on the first day of using the dietary supplement and, in a few cases, on the initial use (62 FR 30684). Overall, the reported signs and symptoms associated with these AER's included those in which clinically serious events occurred, including heart attack, stroke, psychoses, seizure, and in a few cases, death, as well as those with less clinical significance, including rapid and irregular heart rhythms, increased blood pressure, anxiety, nervousness, tremor, hyperactivity, and insomnia (62 FR 30683).

The Agency recognized that these reports could be indicative of early warnings of serious cardiovascular or nervous system risks if product use were to continue. Notably, the information from these adverse events revealed consistent patterns of signs and symptoms in both healthy individuals and in those with underlying diseases or conditions. Many of these reported signs and symptoms occurred in young adults who generally would not have been expected to be at high risk for such conditions (e.g., heart attack and stroke). Included were the deaths of two young adult males in which the medical examiners attributed the cause of death to ephedrine toxicity (ARMS Nos. 10862 and 11134 at 62 FR 30720 and 30722, respectively). In some cases, particular events appeared to reflect individual sensitivities related to dose levels, frequency, or duration of use of ephedrine alkaloids (62 FR 30684).

As depicted in Chart C, the ephedra AER's generated an important "signal", but were just one small component (the "tip of the iceberg") of FDA's overall analysis of the potential public health risk associated with this product. To better understand the nature and types

of products associated with these AER's, FDA conducted a review of the marketplace (62 FR 30679). Over a two-year period, FDA collected and analyzed over 25 dietary supplement products labeled as containing a known source of ephedrine alkaloids. FDA also searched the scientific literature for relevant clinical studies, case reports, and the expected physiologic and pharmacologic effects. In addition, FDA also convened an ad hoc working group of its Food Advisory Committee (Working Group) and its Food Advisory Committee to consider the public health problems associated with the use of ephedrine alkaloid-containing dietary supplements (62 FR 30680). In the proposed rule, FDA requested comments containing data, particularly clinical data, on the safety of the use of ephedrine alkaloids in dietary supplements. (62 FR 30694).

As noted above, while the AER's served as the warning signal of potential hazard associated with the use of dietary supplements containing ephedrine alkaloids, the Agency's evaluation of those hazards was comprised of multiple sources of scientific information. This evaluation included the AER's, a search of the scientific literature, published case reports, controlled clinical studies, and published reports of adverse events associated with traditional uses of ephedrine alkaloids. All of these sources of scientific information revealed a consistent pattern of cardiovascular and nervous system effects associated with ephedrine alkaloids. That view was affirmed by FDA's Food Advisory Committee.

VII. CONCLUSION

Mr. Chairman, thank you for the opportunity to participate in this public dialogue on passive spontaneous reporting systems. It is my hope that through this forum, you, Members of the Committee, and the public will appreciate both the value and the challenges these systems offer.

To effectively provide us with an early warning signal as to possible public health dangers associated with a given product, these systems need to be healthy. To achieve and maintain healthy systems requires the computer infrastructure to support the data, and sufficient staff with the clinical expertise to review and analyze the data. In addition, it must be recognized that these adverse event reports are but one piece of a postmarketing/risk assessment process. Health care providers, manufacturers, and the individuals must each take responsibility for the contribution they must make to ensure FDA's passive reporting systems continue to provide the value they add to a broader postmarketing surveillance system.

I will be happy to answer any questions you may have.

Appendix

Spontaneous reporting systems – for blood and blood components

The blood bank and source plasma industry submits the majority of error and accident reports received by the Center for Biologics Evaluation and Research (CBER). Most of these reports relate to donor suitability. A proposed rule that published in 1997 would expand the reporting requirement for licensed facilities to include unlicensed blood establishments and transfusion services.

When a blood transfusion (or blood collection) complication is confirmed to be fatal, it must be reported to FDA within 7 days. This information is used for risk assessment and communication of risk to blood establishments, transfusion services, and physicians. Adverse events associated with therapeutic plasma-derivative products (such as hemoglobin) are reported in the same way as adverse events associated with drugs and other therapeutic biological products.

Spontaneous reporting systems – for vaccines

Vaccine Adverse Event Reporting System (VAERS)

Postmarketing surveillance for vaccines is handled by the Vaccine Adverse Event Reporting System (VAERS), a system independent of other FDA spontaneous reporting systems. Established in 1990, VAERS is jointly managed by FDA (CBER's Division of Biostatistics and Epidemiology) and Centers for Disease Control and Prevention

(Vaccine Safety Activity, National Immunization Program). Representatives of both agencies oversee data processing and database management performed by a contractor.

VAERS receives 11,000 to 12,000 reports per year. Approximately 15 percent of the reports describe a *serious* event, defined as either fatal, life-threatening, or resulting in hospitalization or permanent disability. Selected reports of serious events and all reports of fatalities are followed up individually by a health professional, and autopsy reports, as well as other medical records are retrieved when available. Medical staff carefully monitor trends in adverse event reporting for vaccines, with particular attention to newly licensed vaccines. In addition to monitoring reports according to vaccine type, reports are monitored according to the vaccine lot.

Spontaneous reporting systems – for devices

Manufacturer and User Device Experience (MAUDE) Database

In 1984, FDA implemented the Medical Device Reporting (MDR) regulation, which required manufacturers to report device-related adverse events to FDA. In 1990, the Safe Medical Device Act (SMDA) amendments expanded FDA's authority by requiring that user facilities (e.g., hospitals and nursing homes) report device-related serious injuries to the manufacturer and device-related deaths to the manufacturer directly to FDA. The Agency receives approximately 80,000 to 85,000 device-related adverse event reports every year. The bulk of the reports are from manufacturers, with user facilities submitting only about 5,000 of this total. The Manufacturer and User Device Experience

(MAUDE) database, established in 195 to support the SMDA, contains approximately 300,000 reports. Another 500,000 reports are in the pre-1995 database.

When received, reports are first triaged by medical professionals. In general, the criteria for taking action relate to the unexpectedness and seriousness of the event, the vulnerability of the population affected, and the preventability of the event. Reports that involve pediatric death, explosion, and/or multiple injuries from one device, are sent immediately to supervisors of the report review staff for evaluation and further action if necessary. All reports are entered into the MAUDE database, subjected to quality control procedure, and then sent to the clinical analysts for review within 48 hours of receipt. Clinical analysts review and assess the adverse event reports. Each analyst is responsible for products within a specific medical specialty or for products that have common design or material features. Here, as with drugs and biological products, the analysts' experience and familiarity with the products play a significant role in the evaluation of these reports.

Alternative Summary Reporting

To evaluate more effectively the large number of medical device reports, FDA has initiated a risk-based alternative reporting system – *summary reporting*. Products approved for summary reporting are well known with well-documented adverse event histories. This approach consists of the periodic submission of adverse event data in tabular format and provides significant economies for both the device industry and FDA. In the past year, FDA received approximately 30,000 reports in summary format.

Spontaneous reporting systems – for cosmetics and foods

Cosmetic Adverse Reaction Monitoring Database (CARM)

The CARM program was initiated in the Office of Cosmetics and Colors, CFSAN, in 1993. This passive program collects consumer adverse reaction reports received by FDA Headquarters, FDA District or Field Offices, and the MEDWATCH program. CARM program information is monitored as it is received for serious adverse reactions that may require immediate follow-up. The CARM computer database is updated quarterly to add reports received by FDA field offices to those received at the Office of Cosmetics and Colors. Typically, FDA headquarters will receive about 125-150 consumer complaints into a computer database to facilitate review and evaluation. A CARM review committee periodically meets and evaluates adverse reaction summary reports for evaluation and possible follow-up actions. The committee includes compliance staff, a toxicologist, a cosmetic chemist, and program management staff. CARM program follow up action may include requesting field support through inspections, sample collections and consumer interviews. Annual CARM summary reports are available for public release and are provided to the cosmetic industry.

Spontaneous reporting systems – for veterinary products

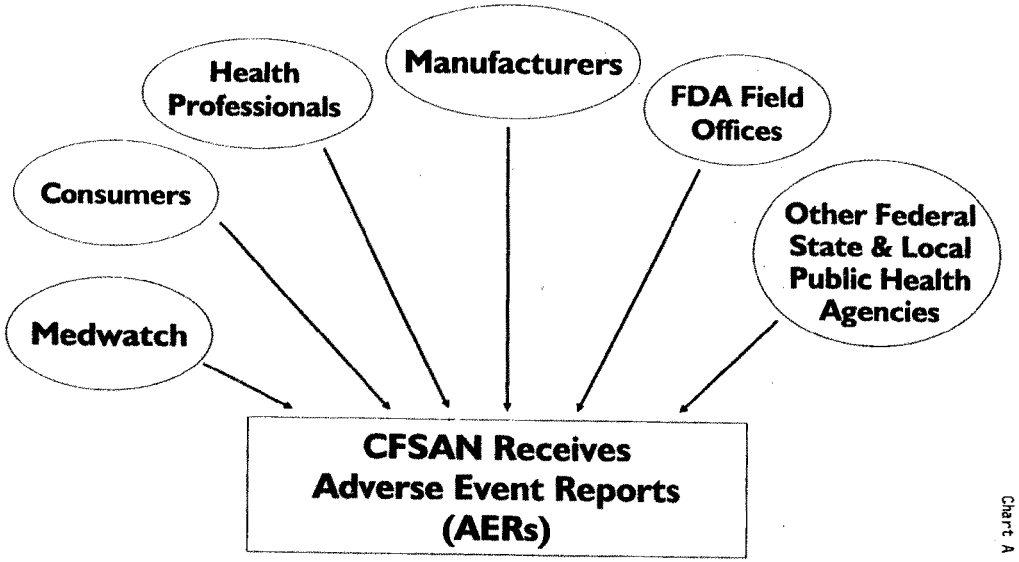
Postmarketing surveillance for veterinary products is handled by the Adverse Drug Events (ADE) database, a system independent of other FDA spontaneous reporting systems. The ADE database receives 4,000 to 5,000 reports per year. The bulk of the reports are from manufacturers. All reports are entered in the ADE database. Medical staff track adverse events, with particular attention to reported adverse reactions that are

not in product labeling. Medical staff will then often meet with manufacturers to discuss label changes based on new adverse reactions or product defects. Label changes are suggested if needed.

Adverse Reaction Monitoring System

The ARMS system was originally established in 1985 to collect and evaluate potential adverse effects to food and color additives, such as aspartame, monosodium glutamate (MSG), and sulfites. Its use was later expanded to cover other specific food products. ARMS is a form of passive surveillance that is designed as a sentinel system to identify specific areas for focused clinical investigations that can evaluate associations between food and color additives and adverse events. The reports, which tend to be acute in nature and related to food allergies/intolerance, or microbiological infections, are classified by severity of the reaction and by the frequency and consistency of the association with ingestion of the product of interest.

Adverse Event Reporting
Special Nutritional Products*

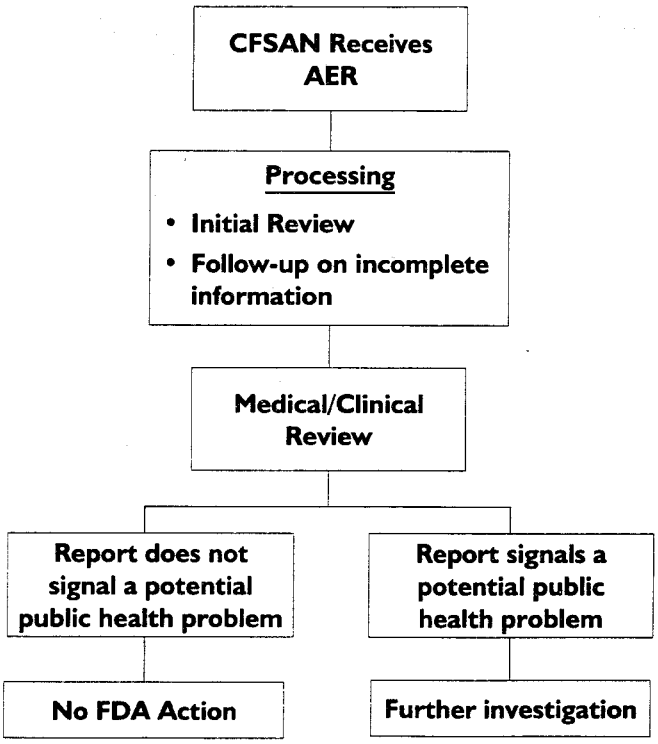


* Dietary Supplements, Infant Formulas, Medical Foods

Chart A

Chart B

CFSAN AER Process
Special Nutritional Products



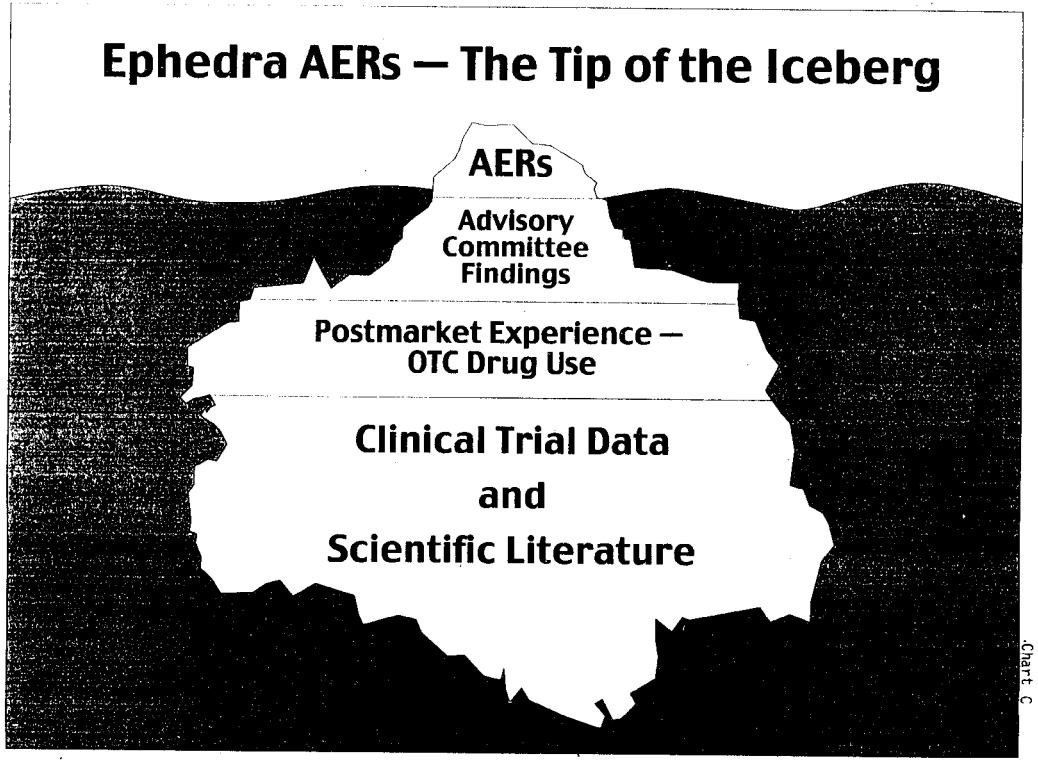

Ephedra AERs — The Tip of the Iceberg
AERs
Advisory Committee Findings
Postmarket Experience — OTC Drug Use
Clinical Trial Data
and
Scientific Literature

Chart C

Mr. BURTON. Why is it that the FDA evaluation reports determine the causality in veterinary medicine for animals but not the dietary supplement for humans?

Mr. LEVITT. I think the question is addressing how we evaluate the strength of the reports. That is really what you are talking about. In your statement you listed two main things. One is seriousness and one is what you referred to as causality. I would like to think of that as attribution or how strong is the association.

Inherently, with any passive reporting system, whether it is veterinary drugs or human drugs, there are going to be limitations in terms of how much information is available to us, both in terms of how much is available and what other activities are present, whether it is other therapies, other medical conditions, special populations. All of those have to be evaluated together.

I think it is, however, a misconception that that is not part of the system as we have it because inherently when our medical staff—we view reports, that is a very important part of what they look at.

One thing that I have, I think, gleaned from, as I have looked more into this recently, is an important lesson from what has happened is that we need to have greater transparency and understanding of the process that we have. And one thing that we will be undertaking will be to describe better what processes that we do use and also how can we refine those processes.

Now, if I can add—to help us do that, we have set up a working group under the auspices of our food advisory committee to address, specifically, adverse event reporting; and this has broad membership of health professionals as well as industry. And this group is just getting going so the timing is very good.

They have two charges which have already been written out. I think after this hearing we will go back and decide if we need to broaden or refine the charge because the timing is too good not to take advantage of that. But the charges are twofold.

No. 1, to identify medical toxicological and communication principles or guidance that could assist industry in establishing and implementing a system to solicit, collect, evaluate, and report potential safety concerns associated with product purity and consumer complaints and reports of illness or injury. So the first charge is what are things that the industry should be looking at to do better.

The second is directed to FDA. Based on your knowledge or experience in other food safety or food science arenas, could you please suggest mechanisms for FDA to share post market surveillance information with consumers, the dietary supplements industry, the medical community, and other surveillance system.

So as I said, this group is being assembled right now and I think that we should take advantage of what is learned today and feed that back in so we can have recommendations.

Mr. BURTON. I glean from your answer that you are going to be doing that in the future, and in the past you haven't.

Mr. LEVITT. What I am trying to say is that in the past, that has been more a part of the process of internal evaluation, and it has been obvious to outsiders because it hasn't been designated to 1, 2, 3, 4.

But when I talk to the reviewers and ask them how do you evaluate the reports, one of the most important elements that they look at is how strong or how weak is the association with it. And I think we need to clarify that.

For example, when we later talk about ephedra, there are large numbers of reports that are often reported, saying FDA has so many reports, and that is so. However, FDA within the internal analysis breaks those down much more and tries to look at that.

So we need to spell out where and how we do it so it is better understood. And if we are not doing it as well as we should, we should improve that, too.

Mr. BURTON. Thank you. One of the things that concerns me—and I mentioned it in my opening statement—is that things are posted on your website and they may or may not be accurate. The information that you have on there may be a conclusion that is reached, but it takes a year or more for that to be clarified or removed. During that time the company that may be the "victim" or the person who suffers from this, may not be able to get that clarified, and it may hurt the sale of their product at the marketplace. During that time many companies have had difficulty getting the FDA to respond to them to clear up these misunderstandings.

I know that my time has expired, and I will talk more about this in a second round. One of the things that concern me—I take Slim Fast. I know I look thin, strong, healthy and everything—why is it that nobody is smiling at that?

In any event, if you look at the website that you have, you show approximately 22 problems that are created by Slim Fast that may or may not be accurate and probably hasn't hurt because people still continue to use it, but could hurt a product like that in the marketplace.

And during the time that a company is trying to explain to the people that buy it, who might be scared to death after reading something like this on the website, they have no recourse because you are not having a dialog with them and getting it cleared up.

So what's the answer to that?

Mr. LEVITT. I think the answer to that is that we at the FDA need to have a greater sensitivity to the manufacturers in this whole process. We have focused primarily on our internal work. The reports come in. We try to look at them, and making time and resources available for getting the reports FOI purged and ready to submit has taken a back seat.

Earlier this year, when that was brought to my attention, we have allocated funds this year but we are terribly behind and it will take us some time to catch up.

But if I were to paint a picture of the way that I would like to see it, we need to have a system so that as with other product centers, if you look around within FDA, reports come in; they go through the normal purging for names and identifiers of health professionals and patients if they are there, and they are sent to manufacturers because the manufacturers have an important role to play, not just in knowing what is there but in helping and investigating what is going on with this product. And that's something we have to try and fix.

Mr. BURTON. I want to go ahead and yield to Mr. Waxman, but let me just say that I think that's something I would like to work with you on, and I think the committee would like to work with you to make sure that businesses who may have been hurt by misinformation that has been put on the website or public, into the public domain, have quicker access to the FDA so they can clarify those things so they don't suffer.

If a product is bad, it should be off the market. We don't want it to hurt the people. But at the same time in the free enterprise system, we want to make sure that businesses don't suffer either because of erroneous information put on the website that they can't get off, and work with you to clarify those things.

Mr. Waxman.

Mr. LEVITT. Yes, thank you. And we need to be working more closely with companies on their followup.

Mr. BURTON. OK.

Mr. LEVITT. So that we can have a stronger system.

Mr. WAXMAN. Thank you very much, Mr. Chairman. One of the most fundamental safeguards of public health is adverse event reporting. An adverse event is a death or serious disease or injury that's linked to the use of a drug, a medical device, or a dietary supplement. Adverse event reporting is required of some product manufacturers but not of manufacturers of dietary supplements.

Can you explain why adverse event reporting is so important to protecting the public health?

Mr. LEVITT. Well, with any product, even those that have premarket testing and review, once the product gets onto the market, it is exposed to many more people, many different kinds of people, people that are taking different kinds of medications, have different medical conditions, and any premarket system is not going to be able to pick up rare events, interactions or other things that control trials cannot do.

When you have a system such as here, where there is no premarket, that is even more important because that is the way that we can pick up signals that there may be a problem with the product. And so we need it as a critical feature to signal us, hey, there may be a problem with this product; FDA, you need to look into it; you need to work with the company and say maybe we need to do something to improve things.

Mr. WAXMAN. If a drug is on the market, and it has already gone through an approval process where FDA assures the safety and efficacy of that drug, is the manufacturer of the drug required to report adverse impacts from the use of the drug?

Mr. LEVITT. In the context of prescription drugs, yes, manufacturers are required to report to FDA all adverse events that they receive associated with their product. They have to report on a more urgent basis those that are serious and unexpected, meaning not on the product label; and later on, more routine reports. But, yes, they are required to submit those.

Mr. WAXMAN. How about medical devices such as x-ray machines or artificial joints; does the law require the manufacturer of medical devices to report adverse events?

Mr. LEVITT. Yes. Medical device manufacturers are required to report. The definitions are a little different, but by and large, it is

an attempt to require the submission of important serious adverse events to the FDA.

Mr. WAXMAN. Now dietary supplements, however, are governed under different rules. Can you tell us whether manufacturers are required to inform FDA if they learn about an adverse event report?

Mr. LEVITT. There is no requirement that manufacturers make those submissions to us.

Mr. WAXMAN. This, as you pointed out, is like a double whammy. With other products, you have to assure the safety and in many cases the efficacy before the product can be sold. Dietary supplements can go right on the market without any scrutiny by FDA in advance. But even manufacturers of those products that had to be preapproved before they could be marketed are required to report when there is an adverse event. But dietary supplement manufacturers are not required to report an adverse event to you. They are, however, encouraged to do it voluntarily; isn't that true?

Mr. LEVITT. That is correct, as are health professionals. We probably need to strengthen our outreach there to get as many high-quality significant reports as health professionals are coming across, as well as to the industry.

Mr. WAXMAN. Well, it seems to me this puts a good manufacturer at a disadvantage because it makes it impossible for a consumer to know which products have been manufactured responsibly and which products have not. Would you agree?

Mr. LEVITT. That is correct.

Mr. WAXMAN. Now, under the Dietary Supplement Health and Education Act, we have a voluntary system of reporting adverse events. This means that if a dietary supplement manufacturer learns of a problem associated with its product, there is no obligation to report the problem to the FDA. Are you aware of any situations of manufacturers not reporting problems about its product to the FDA?

Mr. LEVITT. We don't have direct evidence, information, on that one way or the other. Also, unlike the other systems, manufacturers are not required to register with the FDA.

Mr. WAXMAN. If they don't tell you, you don't know?

Mr. LEVITT. That's correct.

Mr. WAXMAN. Well, let me tell you and everybody else here that my staff is doing some research on this issue, and they talked to the people in the State of Texas where they found that there were manufacturers and distributors who had received a large number of complaints about their products.

In fact, I have for the record a list of some of these adverse impacts from the use of the products. One company received over 150 complaints of side effects, including complaints of high blood pressure, kidney problems, difficulty in breathing. Another company received complaints that their product had been linked to at least one heart attack and one case of seizures. Many of these complaints even came directly from doctors' offices, where the doctor learned about what was happening to the patient and called the manufacturer and said, "You better know that your product is causing these distressing events."

While many of these complaints went to the manufacturer, we found out from the Texas Department of Health that the companies didn't share these complaints with the public or the Texas Department of Health until they were compelled to do so by a court.

And I would like to ask unanimous consent to put in the record at least a summary of some of these complaints I doubt you ever heard about these complaints unless you found out about them after the court case. But the manufacturers weren't rushing to report voluntarily what they, in my view, should have been required to report under the law, if the law had been drafted the way it should have been.

Mr. BURTON. Would the gentleman allow us to put a sampling of those along with the number that you have?

Mr. WAXMAN. Mr. Chairman, I ask unanimous consent that they be put in the record at the discretion of the chairman. You can go through them and determine whatever is appropriate to get the point across.

Mr. BURTON. Very well.

[The information referred to follows:]

Documents Obtained by the State of Texas from Manufacturers of Ephedra Products

In 1995, the Texas Department of Health filed suit against the manufacturers of certain ephedra products. The suits were sparked by the large number of complaints the Department was receiving from consumers about side effects associated with the products.

During the course of those lawsuits, the Department obtained documents from the companies that described complaints they had received from consumers and distributors. The following documents are summaries of the documents produced by the Texas Department of Health. The documents show that the companies in question received hundreds of complaints from consumers and distributors about adverse side effects associated with their products. Some of those complaints linked the companies' products to potentially severe side effects, including heart attack, seizures, and facial paralysis. According to the Texas Department of Health, the companies never shared this information with the public or with public health authorities until compelled to do so by a court of law.

The raw documents that support the summaries are avaliable from the Texas Department of Health, and are on file with the committee's minority staff.

Summaries of Product Return Reports - Alliance USA (Formula One) F-6

DATE	DETAIL
11/22/93	MADE ME REAL NERVOUS AND DID NOT LOSE ANY WEIGHT.
11/24/93	MADE ME VERY NERVOUS.
11/25/93	CANNOT TAKE THIS PRODUCT. IT MESSES WITH MY BLADDER.
11/30/93	MADE SICK
	PLEASE REPLACE WITH ONE BOTTL OF F-1 OR F-2
12/01/93	MADE ME SLEEPY.
12/03/93	MADE HER JUMPY, BOTHER HER SLEEP
12/07/93	CUSTOMER SAID IT MADE HER VERY NERVOUS AND JUMPY
12/08/93	UP SET STOMACH.
12/09/93	ILL FEELING AFTER INJESTION.
	UPSET STOMACH.
12/10/93	HAD A HEART ATTACK APPROX I MONTH (DR SAID NO PILLS)
12/15/93	BECAME CONSTIPATED.
12/20/93	IHAVE TO INFORM YOU THAT I MUST CANCEL MY CONTRACT. WHEN TAKING F-1 WITH MY OTHER MEDICATION. I BROKE OUT IN A RAS THAT LASTED SEVERAL DAYS. I TRIED IT TWICE TO MAKE SURE THAT'S WHAT WAS CAUSING IT.
12/28/93	BROKE OUT IN RASH.
12/29/93	MADE ME FEEL DOWN AND TIRED.
01/02/94	1-FORMULA ONE
01/04/94	PAINS IN STOMACH, UNEASY FEELING, TOO NERVOUS
01/10/94	FELT CAFFEINE MADE HER NERVOUS.
	PROSTATE FLAIR UP AND CAFFEINE MADE ME VERY MUCH ON EDGE, NOT SLEEP.
01/13/94	DIDN'T LIKE IT.
01/16/94	MADE MY HUSBAND SICK.
01/20/94	MADE MY STOMACH UPSET.
01/21/94	FORMULA ONE
01/24/94	MADE HER TIRED- SHE FELT WORSE ON THE DAYS SHE TOOK F-1.
01/27/94	FORMULA ONE
01/28/94	FORMULA ONE

F-

DATE	DETAIL
01/31/94	GOT HIM TIRED AND UPSET STOMACH.
02/04/94	SHIPPING/CHECK
02/06/94	TO TERMINATED THE DISTRIBUTERSHIP WITH ALLIANCE. WAS LEAD TO BELIEVE AS A INDEPENDENT DISTRIBUTER I WOULD HAVE EXCLUSIVE RIGHTS TO MARKET THESE PRODUCTRS. I HAVE SEEN THESE PRODUCTS IN RETAIL STORES. I HAVE EXPERIENCE PHYSICAL DISCOMFORT WHILE TAKING THIS PRODUCT AND WILL NOT RECOMEND IT.
02/10/94	COSUMER WAS GETTING HEADACHES.
	PILLS MADE ME SHAKEY.
02/11/94	MADE HER TO NERVOUS TO TAKE
02/17/94	DID NOT LIKE THE SENSATION THAT I WAS GETTING LATER ON.
	FORMULA ONE
	INCREASE APPETITE, MADE ME ILL.
	SORE THROAT, TOOK ONE AND MADE ME HUNGRY. TOOK TWO PILL, MADE ME JITTERY.
02/19/94	FORMULA ONE
02/21/94	DIZZY,NAUSEOUS, HEADACHES
02/23/94	AS YOU CAN SEE THIS BOTTLE IS BURNED, RTN FOR REPLACEMENT. RPA 9917552. I FULL DAMAGE BOTTLE RTN.
	MADE ME HYPER
02/24/94	THIS MAKE ME VERY SHAKEY AND NERVOUS, KEEPS ME AWAKW AT NIGHT.
02/25/94	EXPERIENCE SIDE EFFECTS FR F-1.
	EXPERIENCED SIDE EFFECTS FR F-1 WANTS REFUND.
	FORMULA ONE
	RTN, DID NOT WORK
03/01/94	
	FORMULA ONE.
	MAIL REF MEDICAL PROBLEM WITH F-1
03/02/94	RTN BOTTLE OF F-1, CUSTOMER RTN, HAD A REACTION.
03/05/94	FORMULA ONE
03/07/94	CUSTOMER COMPLAINED OF HEART RACING.
	DIZZINESS

DATE	DETAIL
03/10/94	SHE SAID SHE DID NOT LIKE HOW SHE FELT AFTER TAKING. SHE SAIS SHE FELT LIKE SHE WAS HAVING AN OUT OF BAD EXPREIENCE, DID NOT FEEL WELL.
03/11/94	FORMULA ONE.
03/12/94	DIZZYNESS, NAUSEAT
03/13/94	RECOMMENDED DOSAGE DID NOTHING, INCREASED DOSAGE, MADE NAUSEATED, DECREASE BACK TO RECOMMENDED DOSAGE, TOOK THE REST, STILL DID NOTHING.
03/15/94	DIZZINESS, NAUSEOUS
	RTN BOTTLE OF F-2, CUSTOMER CLAIMED GAVE HIM HEADACHE.
03/21/94	F-1 MADE ME VERY SLEEPY, THEN I TRYED TO TAKE IT A DIFFERENT WA THE SALES LADY SUGGESTED ME TO TAKE. I GOT REAL SICK TO MY STOMACH AND I STILL WAS VERY SLEEPY
03/24/94	MESSED CLIENTS STOMACH UP.
03/25/94	ASSOC CALLED TODAY, CONCERNED ANOTHER ASSOC SOLD FORMULA ONE TO A FRIEND AND THE FRIEND CAME UP POS ON DRUG TEST AND WAS TERM FR JOB.
03/28/94	CASUSED HIGH BLOOD PRESSURE.
	CUSTOMER HAS DIZZINESS. PLEASE REP.
03/29/94	WANTS PRODUCT REFUNDED 1 BTL F-1. LADY HAS HIGH BLOOD PRESSURE AND THEY MAKE HER FEEL LIGHT-HEADED. THIS LADY IS IN HER 70'S.
03/30/94	MADE ME FEEL LIKE MY HEAD WAS IN VISE.
04/05/94	SHIPPED 1 BTL F-1.
	SHIPPED BTL F-1
04/20/94	RTN BTLS, MAKING COSTUMERS JITTERY, AND IT DOESN'T GIVE THEM ENERGY.
04/21/94	CUST OF ASSOC CAME UP POS IN DRUG TEST AT WORK. SHE SENT A COPY OF INFO CONNECTION ABOUT F-1, AND THEY WILL NOT LET HIM RTN UNTIL THROUGH WITH COUNSELING. HE MUST COME UP POS FOR SOMETHIN(ELSE OTHER THAN A PO/NEG ON AMPHETAMINES
	CUSTOMER CAME POS ON DRUG TEST, SHE SENT THEM A COPY OF CONNECTION, BUT SHE WILL STILL HAVE TO GO TO COUNSELING. COULD SHE COME UP POS FOR SOMETHING ELSE OTHER THAN AMPHETAMINES.
04/22/94	ASOC CALLED SAID THAT F-1 WAS GIVING HER HEART PROBLEMS, ASKED HER IF SHE CONSULTED A DR, SHE HAD. SUGGESTED TO HER TO GET A LETTER FR DR, AND SEND TO MARKETING. SHE DID NOT WANT TO DO THAT. SHE SAID THAT SHE WAS GOING TO TELL HER D/LINE AND CUSTOMERS THAT F-1 WAS BAD FOR YOU. TOLD M.T. & T.L.

DATE	DETAIL
04/22/94	ASSOC CALLED AND SAID F1 WAS GIVING HER HEART PROBLEMS, ASK IF SHE CONSULTED A DR. AND MINE SENDING A LETTER FR DR. SHE SAID SHE CONSULTED A DR, BUT WOULD NOT SEND A LETTER. SHE SAID SHE WAS GOING TO TELL HER CUSTOMERS AND DOWNLINERS THA FI WAS BAD.
04/29/94	ASSOC COMPLAINTED OF ALLERSIC REACTION, RASH FR F-1.
	CALLED ASSOC TO ADVISE OF THE MA HUANG EFFECT ON DRUG TEST. SEN HER SOME INFO ALSO. GAVE TO LARRY WILLIAMS FOR TRAINING.
	CALLED ASSOC TO ADVISE OF THE MA HUANG EFFECT ON THE DRUG TESTING, SENT HER SOME INFO, ALSO GAVE THEW INFO THE GEOF TO GIVE FOR TRAINING
	CALLED ASSOC TO ADVISE OF THE MA HUANG EFFECTS ON DRUG TESTING, ALSO SEND HER SOME INFO. ALSO GAVE THE INFO THE GEOF TO GIVE T THE FOR THE TRAINING.
	CUSTOMER OF ASSOC COMPLAINED OF ALLERGIC REACTION, RASH FR TAKING F-1.
05/04/94	RETURNING BOTTLE OF F1, CUSTOMER GETTING SICK, ASSOC GAVE HER MONEY BACK
	RT TWO BOTTLE SAYING THEY CAN'T TAKE. REPLACE WITH TWO MORE.
05/06/94	ASSOC HAS BEEN EXPERIENCE PROBLEMS WITH CONSITPATION
05/09/94	ASSOC IS RESIGNING BECAUSE PRODUCT MADE HIM SICK.
	RECD 1/2 BOTTLE . SHIPPED 1 BTL F-1.
	RTN 4 BOTTLES F-1, REASON RTN, CUSTOMER NOT SATIFIED WITH IT.
05/10/94	ASSOC IS RTN BOTTLE OF F-1, CUSTOMER WAS NOT HAPPY WITH PRODUCT.
	RTN, COULD NOT TOLERATE
05/11/94	RTN I BTL TO ADDRSSS ABOVE
05/13/94	DENVER, DR DAVID PATE, ST LUKES HOSPITAL ON HOUSTON CHANNELS-REF MA HUANG AS EPHEDRINE, PUT SEVERAL PEOPLE IN HOSPITAL, SAYS VERY DANGEROUS DRUG.
	NEW ASSOC TO RESIGN AND REQUEST REFUND F-101 MAKES HER SICK.
05/16/94	REC I BTL FOR REFUND
05/17/94	GIVES HEADACHES, NO LONGER WANTS.
	SENT ASSOC I BTL AT ADDRESS ABOVE.
	WANTS TO KNOW IS GIVE TO HER SMALL CHILDREN?
05/18/94	WANT TO KNOW IF PEOPLE WITH HYPERTENSION SHOULD TAKE F-1. ALSO IF WE CAN MARKET THE CANADA F-1 FOR THOSE THAT DO HAVE

F-

DATE	DETAIL
	HYPERTENSION.
05/23/94	MAILED LETTER, THANKS FOR INPUT.
05/24/94	SENT ASSOC 1-BTL F-1
06/07/94	ASSOC RTN BOTTLE OF F-1, CUSTOMER SAID IT MADE HER HEART RACE.
	THE FOLLOWING IS TO TERMINATE MY ASSOC WITH ALLIANCE USA DUE TO THE RECENT REPORTS ON THE BANNING OF THE PRODUCT AND BECAUSE COMPLAINTS FR CUSTOMERS ON ILL EFFECTS FR TAKING THE PRODUCT.
06/09/94	
06/21/94	
06/27/94	I HAVE BEEN TAKING F-1 FOR APPROX SEVEN TO EIGHT MO SLOWLEY INCREASING THE DOSAGE UNTIL MAXIMUN. I AM NOT TAKING OTHER TYPE OF MEDICATION OR NUTRITIONAL SUPPLEMENT SO I SUSPECT THE F-1 IS CAUSING MY SEIZURE. YOU DENIED THAT ANY OTHER PERSON REPORTED THIS. I HAVE RESEARCHED THE INGREDIENTS IN F-1, NOW SUSPECT IT MORE STRONGLY. REQ REFUND AND PAY HOSPITAL BILL.
07/05/94	ASSOC WAS GIVEN INFO.
07/06/94	GAVE RAP FOR I BOTTLE F-1`, CUST GOT SICK FR TWO BTLS.
07/07/94	
07/14/94	ONE OF MY CLIENTS HAS BEEN F1 ABOUT 6 WEEKS. SHE WAS TAKING F1 AND BODY WISE CALLE OXY G. AFTER TWO WEEKS OF TAKING PRODUICTS, HAD A REACTION, RAPID BREATHING, ELEVATED HEART RATE, AND BEFUDDLEMENT. ENCLOSING BREAKDOWN OF INGREDIENTS IN OXY G.
	REC I BTL-101 GOT V-REFUND, KEEP FOR EMPLOYEES USA. PLEASE SEND 1BTL #101
07/15/94	CUSTOMER OF ASSOC EXPERIENCED SIDE EFFECTS TAKING F-1 AND ANOTHER PRODUCT BY BODY WISE. WOULD LIKE INFO ON THIS AND INCLUDE INGREDIENTS OF OTHER PRODUCT FOR RESEARCH. SEND FWD TO JESIKA.
07/19/94	CAUSING HEADACHES.
	QUESTION ABOUT F-1 AND INSURANCE.
	QUESTIONS ABOUT FI AND INSURANCE.
	SENT AASOCC 1-910 NEW ORDER
07/28/94	CUSTOMER TESTED FALSE POSITIVE FOR DRUG TEST WHILE ON F-1. ASSOC SUGGESTS ALERTING ASSOC VIA BOTTLE LABING OR LITERTURE (ADVISED ASSOC TO LET CUSTOMERS ALERT EMPLOYERS THEY TAKE F-1 (PRIOR TO TESTED)
	CUSTOMER TESTED POS ON A DRUG TEST WHILE ON F-1. ASSOC SUGGESTS ALERTING ASSOC VIA BOTTLE LABLING OR LITERATURE. ADVISE ASSOC TO LET CUSTOMERS ALERT EMPLOYERS THEY TAKE F-1

F-

DATE	DETAIL
	PRIOR TO TESTING
	MAIL REQ MEDICAL PROBLEM WITH F-1 WANTED IT WITHOUT MA HUANG.
08/01/94	SPOKE WITH ASSOC, WE DO OFFER F-1 IN US WITHOUT MAHAUNG. REQ IF RECONSIDER, THE PRODUCT HAS DONE WELL FOR HER, BUT HAS A SERIOU REACTION TO MA HAUNG, SPENT TWO DAYS IN HOSPITAL FR REACTION.
08/02/94	STATES, MAKING STOMACH UPSET, CAUSING VOMITTING, WANTS EXPLAINATION.
08/03/94	QUESTION REF TO F-1, ONE OF MY CUSTOMERS WAS TAKEN F1 AND FEELING GO, BUT HER DR TOLD NOT TO TAKE IT BECAUSE IT WAS INCREASING HER BLOOD PRESSURE. I THOUGHT THAT F1 DECREASED NOT INCREASED. GIVE ME SOPME ADVISE.
08/15/94	REQ INGREDIENTS AND AMTS IN PRODUCT PER ASSOC THERE ARE MANY CONFLICTING STORY FR ANOTHER NETWORK THAT FDA IS CLOSING US DOWN. INFORM HER THAT IS NOT TRUE. SHE WOULD LIKE TTHIS IN WRITTING, ASSOC WOULD LIKE THE BREAKDOWN IN INGREDIENTS IN F-1.
08/17/94	PASTOR COMPLAINS THAT F-1 DID HARM TO ONE OF HIS CHURCH MEMBERS
	RPA FOR I BOTTLE F1
08/18/94	ASSOC RPA RTN UNUSED PRODUCT CUSTOMER COMPLAINTED.
08/19/94	MARIE GUESS(NOT CORRECT SPELLING) IS A NURSE WHO HAS A PATIENT WHO TAKES F-1 WITH HEALTH PROBLEMS, SHE WISHES TO KNOW THE INGREDIENTS AND WISHS TO KNOW IF THERE IS A TIME LIMIT OF TAKIN THE PRODUCT.
08/22/94	RTN 3 BTL OF F-1 FR TWO DIFFERENT CUSTOMERS WHO COMPLAINED OF HEADACHES. AT ASSOC REQ, FAX RPA.
08/29/94	SELLING TO NURSES, NEED INFO.
08/31/94	ASSOC RTN ONE BOTTLE MADE CUSTOMER SICK.
	REQ BREADOWN OF F-1.
09/01/94	LETTER REC'D DR ADVISED STOP TAKING F1, HAD NEG RPT, BLAMES F1. WIFE ALSO TOLD TO STOP, INCREASED BLOOD PRESURE LETTER ADD TO DI RONA.
	REFUND EMP SHIP SHIPPED ON ORDER 330838
09/02/94	CUSTOMER SICK RTN FOR EXCHANGE.
	GAVE INFO TO ASSOC, THERE IS 30MAG OF COMBINE CHROMIUM IN F-1. ONLY INTEREST IN F-1
09/07/94	REFUND EMP

DATE	DETAIL
09/07/94	REFUND EMP.
09/08/94	CUSTOMER TESTED FALSE FOR ATHLETE DRUG TEST. SUSPENDED 6 MO. NEEDS INFO ON PRODUCT. ADVISE FAX LETTER TO D. SMOTHERS
	IT MADE ME VERY NERVOUS.
09/09/94	SHIPPED ON ORDER 3400354
09/12/94	UNREADABLE
09/13/94	WANTS A REFUND FEE AND TERMINATE REVENUE SHARING PLAN. CAN NO TAKE PRODUCT, IT MAKES ME FEEL BAD. CONSEQUENTLY I COULDN'T CONTINUE TO SELL THE PRODUCT.
09/19/94	BECAME VERY ILL, NERVOUS, VOMITING, JITTERY.
09/20/94	FORMULA ONE.
09/26/94	SICK
09/27/94	ASSOC HAS RESIGNED DUE TO F-1. SEVERAL PEOPLE HAVE HAD VERY B REACTIONS TO F-1. SHE FEELS THE REST OF OUR PRODUCTS ARE GOOD, BUT CAN'T REPRESENT A CO WHO SELLS A PRODUCT LIKE F-1.
	RTN, WITH FORMS,VARIOUS REASONS, MADE SOMEONE NERVOUS, AND MAD ME SICK TO THE STOMACH
10/05/94	AFTER TAKING THE PRODUCT FOR A FEW DAYS, I BECAME EXTREMELY ILL AND WAS IN BED FOR FOUR TO FIVE DAYS. LOST FOUR DAYS WORK. MY HUSBAND HAS BEEN TAKING THE PRODUCT 2-3 WEEKS AND HAS BEEN UNABLE TO LOSE WEIGHT.
10/06/94	ASSOC IS RESIGNING BECAUSE SHE GOT A VERY BAD RESPONSE FR.
	WOMAN PHONED IN SAYING SHE IS HEALTH PROFESSIONAL WHO HAS 3 PEOPLE WHO HAD SEMI HEART ATTACKS CLAIMING TAKING F-1 AND WE AN WE ARE THE RESPONSIBLE PARTY. WANT TO KNOW WHAT INGREDIENTS ARE. SHE IS FINDING CHROM PICOLINATE, BORON PROTINATE. FINDING SOME ORIENTAL AND OTHERS. SOME ONE NEED TO CCALL HER BACK IN ONE HOUR.
10/13/94	PLEASE REFUND THIS LADY'S FEE.
10/15/94	MADE HER SICK TO HER STOMACH AND THREW UP.
10/16/94	FORMULA 1 DID NOT LIKE.
10/22/94	COULD NOT GET OVER THE NERVOUS FEELIONG AFTER TAKING FOR ABOUT THREE WEEKS.
10/27/94	
	FORMULA ONE
	HAD NO EFFECT

DATE	DETAIL
11/02/94	UPSET HER STOMACH.
11/11/94	FORMULA ONE
11/15/94	FORMULA ONE
11/22/94	FORMULA ONE. CASH
12/04/94	
12/10/94	HIGH BLOOD PRESSURE
12/22/94	AFTER TAKING F-1, I STARTED HAVING CONSTIPATION WHICH NEVER WEN AWAY
12/28/94	BTL OF F1 TAMPERED WITH. CONTAINED THREE (3) FOREIGN WHITE PILL
01/04/95	BTL OF F1 TAMPERED WITH. CONTAINED THREE (3) FOREIGN WHITE PILLS. REPLACEMENT BTL SENT, APOLOGY.
01/05/95	BTL OF F1 TAMPERED WITH. CONTAINED THREE (3) FOREIGN WHITE PILLS. REQUEST FOR ANALYSIS OF PILLS.
01/09/95	RE: ASSOC CALLED IN REGARDS TO BOLT SHE NEED TO RETURN SAYS CUSTOMER SAY THE PILLS SMELL BURN AND HAD BROKEN SEAL
01/24/95	RE: BROKE OUT IN RASH AROUND FACE AND EYES
	RE: SAME AS 5236
03/25/95	ASSOC CALL TODAY CONCERNED, ANOTHER ASSOC SOLD F-1 TO A FRIEND, WHO TESTED POS IN A DRUG TEST WAS SUSPENDED AND TERMINATED FROM HER JOB.
03/29/95	REQ INFOR STATING NO ANAMIAL PRODUCTS IN IT.
07/14/95	CAN'T READ
07/17/95	CAN'T READ
10/15/95	FORMULA ONE

F

DATE	DETAIL
	RESPONSE
NOT DATED	I BECAME AN ASSOC 18 AUG 93, BUT ALL THE PEOPLE I WORK WITH ARI MY MAIN CONTACTS, WILL NOT TAKE THE PRODUCT ANYMORE. THEY FEE THE PRODUCT NOW MAKES THEM GRUMPY AND MOODY, ALSO THEY JUST DON'T LIKE THE WAY THEY FEEL UP AND DOWN. SO PLEASE REFUND MY MONEY.
	I HAVE TRIED THREE TIMES TO TAKE FORMULA ONE. EACH TIME I BECA SICK AT MY STOMACH.
	I JOINTED ALLIANCE PRIOR TO TAKING F-1. I EXPERIENCE ADVERSE REACTIONS TO SAID PRODUCT AND CAN NOT TAKE IT. I CAN NOT IN GO FAITH REPRESENT A PRODUCT TO OTHERS,WHICH I CAN NOT TAKE MYSEL
	LOST INCHES AND WEIGHT, BUT HAD A SERIOUS REACTION TO MA HUANG. TWO DAYS IN HOSPITAL FR REACTION.
	LOST INCHES AND WEIGHT, BUT HAD SERIOUS REACTION TO F-1. HOSPITAL FOR TWO DAYS FR REACTION, PLEASES ASSIST.
	MADE ME FEEL WIRED.
	MADE ME HAVE A NERVOUS REACTION
	MADE MEMBER TO JITTERY.
	MAKE ME TO MOODY AND ALSO SHAKEY.
	MAKES HIS HEAR BEAT TO FAST.
	MEMBER SAID THE PRODUCT MADE HER MUSCLES STIFF AND SORE.
	ORDER 1108519 RPA FOR CUSTOMER FOR F-1 CYSTITIS SEND REPLACEMEN BOTTLE. ASSOC WAS GIVEN RPA #,TO RTN BOTTLE.
	PRODUCT FAILED TO MEET CUSTOMER'S EXPECTATIONS, CAUSED REACTION
	REGARDING
	REQ BREAKDOWN OF THE F-1 INGREDIENTS PER ASSOC LPEASE SEND INFO ASAP.
	RETURNED
	RTN PRODUCT. HAVE ALWAYS BEEN ACTIVE. STARTED TAKING F-1, MUSCLES GOT SORE, COULD NOT EXERCISE WITHOUT PAIN, AND CALF MUSCLE CRAMPED. I HAVE SINCE QUIT TAKING PRODUCT, AND CAN LIT M ARM WITH OUT PAIN. THE DR COULD NOT FIND ANY PHYCIAL REASON FOR THIS. I CAN NOW BEGAIN TO EXERCISE AGAIN WITHOUT PAIN
	SHE HAS LOW BLOOD SUGAR AND MADE HER SICK.
	SOLD A BOX OF F-1 TO A FRIEND, HER FRIEND TOOK F-1 AND GOT SICK AND WENT TO THE DR. SHE HAD A BACTERIA INFECTION, AND SHE THINK F-1 CAUSED IT. THE BOX WAS BURNED ON THE INSIDE, CAP ALSO WAS BURNED. OTHER PEOPLE REC F-1 AND THEIR F-1 WAS OK.

CUSTOMER PRODUCT RETURN FORM
(SINCE MAY 3, 1995 DECREE AND FINAL JUDGEMENT)

DATE	REASON FOR RETURN
10-31-94	Her husband had severe pains in his testicles after taking Formula One and she had pains in her inner thighs.
1-4-95	"After trying a 4-day sample pack, I was experiencing leg cramps....after talking to a co-worker..., she had the same problem. I stopped taking them, the leg cramps immediately stopped."
1-12-95	Caused heart palpitations
2-2-95	Gives customer stomachache each time product is used. Also, associate and several customers have lupus and feel no physiological benefits from new product, whereas original F1 gave relief.
3-5-95	Made me hyper
3-6-95	Caused impotency
3-10-95	Sick, dizzy, heart race, short breath
3-10-95	"I have tried a couple of times taking this all natural formula but have little success as I have had excruciating headaches and palpations
3-10-95	"...it caused heart palpitations and high blood pressure with myself. As for my friend she suffered from migraine headache for 3 days".
3-13-95	Made customer jittery
3-14-95	Unable to sleep, night sweats, jitters
3-15-95	Side effects--dizzy, lethargic, spotting
3-17-95	Having strange feeling in head
3-17-95	Was getting sick--read article put out by FDA
3-20-95	Had a bad reaction
3-20-95	Made me ill
3-20-95	High blood pressure

3-20-95	Caused headaches
3-21-95	Customer sick
3-25-95	"Niacin rush" and itching of the skin
3-25-95	Made my system become jittery and nervous
3-26-95	Physical reaction
3-27-95	Got heartburn from product
3-30-95	Didn't have a period
3-30-95	Made her heart race too fast
3-31-95	Customers leg hurt
4-1-95	Stomach pains, diarrhea
4-1-95	Stomach ache
4-1-95	Became ill when taking product
4-4-95	Making customer sick
4-4-95	Made me sick to stomach
4-4-95	I and several other clients experienced heart palpitations-racing and anxiety attacks.
4-6-95	Making customer feel sick
4-6-95	Made nervous and too jittery
4-7-95	Chest pains, high blood pressure, kidney problems, severe heart palpitations, irregular heart beat, dizziness.
4-10-95	I became very ill, nauseous
4-17-95	Customer say felt very nervous-jittery
4-19-95	Made hands and face break out
4-19-95	Skin began to burn and became blotchy
4-19-95	Severe headaches
4-19-95	Severe headaches; product didn't work
4-19-95	Hives broke out

4-19-95	Severe headaches
4-19-95	Gets jittery and nervous
4-22-95	Upset stomach
4-22-95	(Patient name) was in the "....." hospital...all because of the trial pack I had sold him. He had gone "schizophrenic".
Undated	Because they cause migraine headaches for me.
4-25-95	Physical problems in my eyes, muscles and cysts in my breasts
4-28-95	Too jittery; caused excessive menstrual bleeding
Undated	Unable to take Formula One due to side effects
5-3-95	Although I enjoyed the effects from taking Formula One, we feel that some medical problems which arose were possibly due to this product.
5-4-95	Thinks it caused her liver damage. Has other medical problems and on other medication.
5-8-95	Made me sick (hypoglycemia)
5-8-95	Did not like the way I felt
5-9-95	Feeling mild headaches and news release
5-9-95	Makes my heart race
5-12-95	21 year old was under Doctor's care for what has been apparently diagnosed as hepatitis.
5-12-95	Extreme energy loss
5-12-95	Stomach ache
5-15-95	Caused blood pressure to elevate
5-16-95	It made me fall asleep alot and tired
5-16-95	She has broken out in hives from head to feet.
5-17-95	Had customer break out in a rash
5-19-95	Had rash break out from Formula One.
5-19-95	Made neck hurt

5-22-95	Made me extremely nervous
5-22-95	Reaction--red, burning
5-22-95	Couldn't sleep
5-22-95	Made sick--upset stomach--blood in urine
5-24-95	She said that 3 people she sold them to are having reactions to the product. She also said one is in the hospital due to F1.
5-24-95	Did not like the uneasy way it made me feel (shaky)
5-24-95	Make feel sick
5-26-95	Gave customer gas
5-30-95	Some of her customers are getting red spots
5-31-95	She had hot flashes and turned red and skin was tingley.
5-31-95	Customer breaking out
6-1-95	Upset stomach
6-5-95	Customer didn't like them, didn't curb her appetite, didn't loose weight, kept her up at night, and gritted teeth constantly.
6-5-95	Customer says it raised her heart beat, and she was afraid to continuing (sic).
6-7-95	Some of her customers have had some bloating and gas
6-8-95	Associate called about having a reaction to the new and improved F1. She had broke out in hives and was ill.
6-9-95	I lose my voice--I went off them--then on again-lost my voice
6-9-95	1. tingling and sweating on scalp along with red blotches on face and hands. 2. red blotches on face.
6-9-95	Tingling skin on face and scalp, burning ears, top of hands and wrists red, swelling and burning, shaky and upset stomach

6-9-95	Red blotches on skin, tingling and shaking
6-9-95	Ears burning, tingling skin, red blotches especially on neck, elbows, and knees, shaking.
6-12-95	Reaction to Formula One
6-12-95	Has 3 people that have broke out in a rash from this last order. She sold three bottles out of this case and all three people broke out.
6-13-95	Spoke to assoc. said she went into the hospital with heart failure due to F-1.
6-14-95	In one or two months I realized that my body was having toxic reactions to this formula and I immediately discontinued taking it.
6-14-95	Associate said 10 of her customers have had a alergic (sic.) reaction to the Formula One
6-16-95	Ulcer to flair up
6-17-95	Irritability/heart palpitations
6-18-95	I felt my ears become extremely hot, and my stomach felt upset. My nose began to swell, and I noticed a rash beginning to form on my elbows and in the crease of my forearm. My face was bright red with a rash, my lips were swollen, and my shoulder and neck were blotched with the rash also.
6-20-95	I noticed the palms of my hands were red and itching. During the next five minutes my entire body became very, red, hot and swollen.
6-21-95	My face feels as if I had poured some type of astringent all over. A very tight hot feeling. I it lasted 15 minutes. Then I started freezing and my hands turned totally white and my fingers went numb.....I have never been so frightened in my life.
6-22-95	States it made her too nervous.
6-23-95	I personally experienced chest pains and a stiffness in the neck while using Formula One
6-25-95	Made me feel too nervous
Undated	Gave her irregular heartbeat

6-29-95	"...too many jitters."
7-5-95	Two retail customers had a "niacin rush" and went into the emergency room at local hospital
7-7-95 "...one	"...having a reaction by 3 people here...". customer....claimed she got hives and stomach pains from them.
7-11-95	Gave customer a rash
7-11-95	Causes rashes and breaking out of skin.
7-13-95	Call from assoc. stated husband and 6 retail customers esperience (sic)
7-14-95	Niacin rush, reported 3 retail customers experiencing this
Undated	All three customers are having medical problems and returned the products on listening to TV reports and reading (illegible)
5-29-95	Four of my clients had a reaction including me. Some of the symptoms were red rashes on both elbows and top of the legs also a bright red color on the face and ears, feelings of numbness on the chin, burning over the body with red spots, and the feeling of being on fire or burning feeling on the face and ears.
5-30-95	I have been experiencing allergic reactions which consist of flushed feeling, turning red in your face and chest, along with a red rash and spots. These symptoms last only a short while; however, several other of my clients have reported the same reactions as I have.....I have also had reports people getting diarrhea from the new Formula One.
6-8-95	I am requesting a full refund due to the side effects...
Undated	"....I went ahead and went to the emergency room because I could not go to the bathroom and the cramping would not go away".
Undated	I have 3 customers who.....recently started breaking out in hives. They stop taking the product and the hives go away. Have there been any other people having this problem? (The hives are horrific)

7-6-95	We have had 3 people become ill with Formula One....all three have had a negative reaction from the pills (1 hospitalized).
7-6-95	"We feel through the problems we have had and going thru and the dangers of this Formula One that we should be reimbursed all money paid into your company and for products. The husband spent the week in hospital in July. The wife has been to emergency 2 or 3 times. We neighter have lost no weight. We took all product as stated. Surely in all we used we should have lost some.
7-7-95	Stomach pains
7-14-95	Shortly after taking the capsules (2 at 10am), I felt a noticeable cramp in my stomach accompanied by a momentary wave of nausea. Then within only a couple of minutes, my face began to burn and sting and break out in a very fine rash and my ears began to ring.
7-18-95	Customer went to emergency room for 4 hours, upset stomach, puffy eyes, spots on arms, real flush
7-20-95	"...it caused me to have an extremely sore tongue."

RESPONSE TO MINORITY SUBMISSION ON TEXAS CASE

During the Committee on Government Reform's May 27, 1999 Hearing the minority raised an issue concerning the failure of one manufacturer of a single dietary supplement product to report complaints to state or federal authorities. The company was Alliance U.S.A. located in Texas, and the product was Nature's Nutrition Formula One. The minority has supplemented the record with a list of the complaints found in the company's files that were not reported to the state.

The minority is apparently seeking to show, through the practices of one company, why mandatory reporting for dietary supplements should be required > for the entire industry. However, this example in fact shows that the current system of voluntary reporting is working even in cases such as this, where a single company chose not to share complaints it had received with state or federal authorities.

Texas authorities received large numbers of reports on Nature's Nutrition Formula One. The reports were filed with the Texas Department of Health and with Texas Poison Control Centers through established channels. Using these reports, state authorities identified that this company's product represented a potential public health threat. As the minority states, "the Texas Department of Health filed suit against the manufacturer[]," and "the suits were sparked by the large number of complaints the Department was receiving from consumers about side effects associated with the products." The end result was that the company was forced to reformulate the product, and the product was therefore effectively removed from the market. The attached document from the Texas Department of Health shows the large number of reports on Nature's Nutrition Formula One that were received in 1994 and 1995, followed by very few reports in 1996 after reformulation occurred.

This case illustrates how the voluntary system of complaint reporting is working to identify problem products. The problem that the Food and Drug Administration (FDA) faces, as the agency admitted at the hearing, is that the complaints that are submitted to FDA under the voluntary system are not promptly reviewed and made public, and are not handled in a scientifically appropriate manner. The hearing and the documents submitted by the minority support the conclusion that FDA's energy should be focused on improving the current system of voluntary reporting. FDA did not ask for mandatory reporting during the hearing, and it is clear that mandatory reporting would only cause additional problems for the agency, in addition to creating enormous and unnecessary burdens on industry.

Mr. WAXMAN. One of the arguments we sometimes hear is adverse event reporting is not needed because dietary supplements are always safe. I want to ask you about that. FDA has received about 1,000 adverse event reports relating to ephedra. About how many of those reports are classified as serious?

Mr. LEVITT. Of the—we have received overall about, I believe the number is about 1,000 reports altogether. The number, total number that is serious, I am going—I am going to give an estimate and then provide for the record something that is more detailed. But my impression, it is in the vicinity of 30 to 40 percent. I could be wrong on that but that is the impression I have from talking—it is a large enough number that it is—that it is of concern to us. It is not by any means all of the reports.

Mr. WAXMAN. My last question to you is: Is it not correct that of those reports, 45 were of deaths?

Mr. LEVITT. There are a number of reports of deaths in there. I don't know if that is the exact number but we could certainly check on that, too.

Mr. WAXMAN. Thank you very much.

Thank you, Mr. Chairman.

Mr. BURTON. I think that we might ask Dr. Henney at some point to sit down with us and discuss some of the issues that have been raised by Mr. Waxman after this meeting to see if something can't be done to clarify some of these issues.

We would certainly like to look into that and talk to her about that.

Mr. LEVITT. I think—I don't know what the right process is but I would hope there is also a process for FDA to obtain access to the adverse event reports if there are safety issues there that we need to know about.

Mr. BURTON. There is a definition of serious side effects for prescription drugs, is there not?

Mr. LEVITT. Yes.

Mr. BURTON. Did you have questions? I am sorry. Ms. Schakowsky.

Ms. SCHAKOWSKY. Yes.

Mr. BURTON. Let me yield to Ms. Schakowsky and I will get back to my questions in just a moment. I am sorry.

Ms. SCHAKOWSKY. Thank you, Mr. Chairman. I don't mind waiting for you.

I wanted to continue the line of questioning that Mr. Waxman was beginning.

You had said that there were 30 to 40 percent that were serious. Actually, we heard—and we also heard that there were about 45 deaths. But what is considered serious? Could you tell us what kind of events are considered serious?

Mr. LEVITT. Yes. The general issues that we would consider serious are as follows, and I think I will just read them to be sure that I get this exactly right.

No. 1 is when the outcome is death, is life-threatening, it requires hospitalization or prolongs hospitalization, causes disability, congenital abnormality or requires intervention to prevent permanent impairment or damage. Those are the general criteria under the MedWatch program.

In addition, within our program, we would add on the following, which says that other medical events that may not be immediately life-threatening but which require intervention to prevent one of the serious medical conditions, meaning one of the MedWatch outcomes I just said, would also be considered medically serious.

So it would—both something where we have reached the outcome as well as something that could lead to it. And we consider all of those to be serious under, if you will, the general categorization of dangerous, critical or alarming.

Coming back just to a point earlier, this is not something that we have been as transparent to the outside world as we should be, and that is something that we will be addressing so that it is clear to everybody. It also is worth noting that in the recently revised regulations for prescription drugs, the definitions are very consistent.

Ms. SCHAKOWSKY. Just to clarify, then, in my own mind, you are saying that while these serious event—these reports are not required—that of the thousand reports, you think probably about 30 to 40 percent are serious. You have read what serious is. I think anyone listening to that would agree that's very serious; and it seems to me that your expression of concern is certainly warranted and that is shared by members of this committee as well and may require some further action. I think it almost certainly would.

FDA has issued warnings to consumers about a number of other supplements besides ephedra, and I want to mention a couple of those. The FDA recently issued a warning about products containing GBL and asked companies to recall the product. According to the FDA press release, GBL is related to 55 adverse events. Can you talk a little bit about what those adverse events were and how serious they were?

Mr. LEVITT. Yes. Well, the GBL is a product that converts itself in the body to a drug referred to as GHB, which is a well-known sedative and not an approved product on the marketplace.

We had, of those 55 events, they all were consistent with each other as being quick after taking the product. About 20 of those were associated with somebody who actually was unconscious, sometimes into a coma. There was also one event that was reported in the context of a death.

In that setting, it was clear, I think, that—to everybody looking at it, we had a clear pattern.

Going back, Mr. Chairman, to your question about causality or attribution, we had a very strong association; we had a known product; we had exactly the same kind of result that would be anticipated from what we know of that product, and we said that product needs to come off the market.

Ms. SCHAKOWSKY. In this instance, it was one death?

Mr. LEVITT. One death reported. One report was based on a death, yes.

Ms. SCHAKOWSKY. In 1998, the FDA issued a warning about 5 HTP, which is found in supplements promoted to treat insomnia, depression, obesity, and for children with attention deficit disorder. According to the FDA press release, 5 HTP contained impurities that are similar to the impurities that were found in L-tryptophan, which was banned because it was so dangerous.

Do you remember how many adverse events were associated with L-tryptophan?

Mr. LEVITT. I am going to ask Dr. Yetley to see how her memory is since that's prior to my involvement.

Dr. YETLEY. That particular issue was one that was related to a report that came out of the Mayo Clinic in which they had analyzed those products on the marketplace and had found the presence of an impurity. As soon as they had raised that issue to our attention, we had our chemist work with the Mayo chemist. They developed a method, they developed a standard method, for it. We met with the industry, shared our information on how to test their products for this particular contaminant.

It is my understanding that the industry has worked hard to look at their products and to assess them. So that was not particularly an issue that came up from the adverse event system but was one in which we were trying to prevent adverse events because we had information about a contaminant.

Mr. LEVITT. If I could just add, I am not sure Dr. Yetley heard the question properly. She reacted to something that happened within the last year or so. If you are reacting—questioning about L-tryptophan which was in the late eighties, there were a number of reports associated with that.

Do you recall the number?

Dr. YETLEY. L-tryptophan is a related but somewhat different product than the 5-hydroxy L-tryptophan.

This was a concern that was raised through the reports of adverse events. We had a number of serious injuries and illnesses. We worked with the manufacturers. They did voluntarily recall those products from the marketplace. We did issue warnings, and there was some research done and we have never clearly resolved whether or not those injuries were due to a contaminant, were due to the product itself or to some interaction within the product, but there was a fairly quick action on the part of the agency and a response by the industry in response to those adverse events.

Mr. LEVITT. Right. There was a sizable number, were there not?

Dr. YETLEY. It was a sizable number. I don't remember the exact number.

Ms. SCHAKOWSKY. If I could just make one more comment. It seems to me then, given these examples, that adverse event reporting can help to resolve these dangers and that we have some good examples of that being the case?

Mr. LEVITT. Yes, absolutely. And that was one of the points I tried to highlight earlier, but thank you for reinforcing that.

Mr. BURTON. Before I yield to Mr. Horn, let me just say that it is my understanding that L-tryptophan, it was because of an adulteration of the product that you had a problem; it was not the L-tryptophan itself?

Dr. YETLEY. It is not clear. The research that was done did not clarify that completely.

Mr. BURTON. But once you worked with the industry and they cleaned up the L-tryptophan to take out the other adulterated products, was it no longer a problem?

Dr. YETLEY. I believe the marketing of that particular product was pretty much limited or restricted to a great degree.

Mr. BURTON. Well, it is still being marketed and used, though, is it not?

Dr. YETLEY. I don't know the current use, but it was not used for quite a long time after that particular period.

Mr. BURTON. It was my understanding that it was because of the adulteration, but we will look into that.

Mr. Horn.

Mr. HORN. Thank you very much, Mr. Chairman. I am sorry I have missed some of the previous presentation.

Let me give you an example apparently that occurred on the website. The FDA reported that a 27-year-old female had nausea, passed out, suffered liver damage as a result of taking Slim NRG Plus, a product containing ephedra. However, the woman had also taken Nyquil and two glasses of wine. A drug screening showed she had also consumed acetaminophen, nicotine and three other drugs.

I guess the question is: What does the FDA do to make sure that the adverse events that it is reporting on its website are actually related to the dietary supplement being listed on the website?

Mr. LEVITT. OK. Thank you for raising that. I got to address only part of that point earlier in response to the chairman's question.

Let us take a moment on the website itself, because I think the website is misunderstood for what it is intended to be. Maybe based on what it is, we need to make changes also, but the website is nothing more than a table of contents of reports submitted to FDA.

We got all of these reports. We need to kind of keep track of them, and a system was worked out with just a minimal amount of information which basically is the product, the company, the nature of the reaction reported, and I guess the ingredient. It is just a line listing, and when you see it it is just one line across the page. That is taken verbatim from the report that comes in, even before there is an evaluation done.

That originally, as I have come to understand it, was the center's way, if you will, of cataloging what came in and then following through and doing a more detailed review.

What has happened over time is there were so many requests for that information, and actually under the revised FOI statute for electronic availability we are actually charged with putting up on the web frequently requested documents, and people are asking for this all the time so it was put up on the web.

From FDA's point of view, it was always understood to simply be a table of contents of what was submitted. The problem, I believe, that we have come up to is not so much that, although maybe there are some issues there, too, but the juxtaposition of what the chairman raised about putting that up now and not being able to make the underlying report available to the manufacturer for very long periods of time. So that is the only thing that is up there.

What is done in other centers is that the initial line listing is up there; but the report is up there, too. And so the manufacturer has access to everything and you have, if you will, a full record.

As I testified earlier, and maybe before you were able to be here, we are seriously behind in our purging, what is called purging, or making those documents publicly available because we have to go through each one and take out any identifying information.

I have authorized funds for a contract to bring us up to speed; but the way it ought to be running, which is the way we will try, resources permitting, to do, is we have got to get all the information available to the manufacturers and up there so that there is a complete and full record and people are not misunderstanding, misusing or hurt by what was originally a table of contents of something that comes in.

Mr. HORN. Well, shouldn't FDA have a disclaimer as to the possible inaccuracies? For example, when they put it up here and say the Slim NRG Plus bit and the fact is they didn't know the woman had taken Nyquil and the two glasses of wine and the five additional drugs—and it seems to me somewhere either the authors are at fault in some medical journal and they should have noted that and have a drug screen and so forth, or at least a patient history.

And it seems to me when somebody tunes in to a government-sponsored website they think this is certainly truth, except for the IRS. But actually I would think the FDA, with its scientific reputation, would want to put a disclaimer on any case it puts up there, that you don't know what else this person had that led to the particular conclusion of that little point in time of a case.

Mr. LEVITT. You are right. In fact, that is at least one thing that we have been doing. It appears at the beginning of the website. I have heard a recent suggestion that maybe somehow it ought to appear——

Mr. HORN. On every case.

Mr. LEVITT [continuing]. On every page, but here there is half a dozen disclaimers. But the one that you are referring to says "There is no certainty that a reported adverse event can be attributed to a particular product or ingredient." The available information may not be complete enough to make this determination. So we have tried to make that disclaimer, and maybe we need to tie it closer to the other information so there is no confusion.

Mr. HORN. If a person is taking numerous drugs and supplements and possibly even alcohol, isn't it reasonable to assume that the medical condition could have been caused by any of those things?

Mr. LEVITT. Yes.

Mr. HORN. One last question here. If a person takes two different dietary supplements and has a serious problem and the FDA only reports that the problem was related to one of those supplements, couldn't the FDA wind up banning or regulating the wrong substance?

Mr. LEVITT. Again, that report you are referring to is simply the ingredient listed by the person sending in the report. It does not reflect FDA's judgment in any manner about whether it is serious, whether it is actually attributed to that ingredient or not.

As I said, it is a line listing of everything that has come in. That's why I said it needs to be joined with the fuller document so that all that information is clearly available and people are not misled that just because somebody reported it, it is necessarily associated and or serious.

At the same time, a lot of them are and it would be of benefit to have the information out there.

Mr. HORN. If there are two different supplements, as we postulated there, it seems as though FDA doesn't try to narrow down the cause of the illness; and the end result of that not being done is that the FDA could wind up banning one substance and it is the wrong substance.

Which would really be the most dangerous, to leave that on or to test it or what, as to which substance might really have been the problem?

Mr. LEVITT. Again, it would be—let me take a moment on this. It would be very unusual for us to make a conclusion about whether a product, say, ought to be on the market or not based on a single report. What we are trying to do is actually quite the opposite. Each report needs to be looked at and followed up on, but then we need to be looking at the reports in the aggregate to say, No. 1, is there a pattern here? Is there a consistency?

So I think the system does have that correction already within it, subject, as I said, we need better transparency if that's not well understood.

Mr. HORN. Thank you.

Thank you, Mr. Chairman.

Mr. BURTON. Thank you, Mr. Horn.

Ms. Norton, did you have any questions?

Ms. NORTON. No questions.

Mr. BURTON. Let me ask just a couple of questions.

Go ahead, Henry, and I will finish up. I will yield to you now.

Mr. WAXMAN. Mr. Levitt, if I could—just so I understand this problem of what is on the website, what do you put on the website, a complaint from a consumer that you haven't checked out? Is that it?

Mr. LEVITT. Every report that comes in, the first step is to simply make a line entry into, if you will, the inbox that says, all right, this is a report. We will assign it a number. We will put on that listing whatever the report says.

Mr. WAXMAN. I think it is a valid complaint if a consumer reports a problem with a product, and it turns out that it may not have been that product at all that caused the problem, but the FDA has posted the complaint on the website.

On the other hand, I think people who have a problem with a product and they are sophisticated enough to go to the website and pull down the information that is there should have some information, even though you may not have reached a complete conclusion.

Now, I gather you have a problem in cleaning up your website because you don't have the resources to do it. How about putting a disclaimer that these are reports that FDA has received but cannot verify? After all, you know, the manufacturers for dietary supplements have a disclaimer on their products saying they make the following claim, but FDA has not approved this claim and so there is a disclaimer that the claim may not be true.

That could be a subject for further discussion, but there is a disclaimer. Why can't you make a disclaimer and continue to post reports so people can get that information?

Mr. LEVITT. We do have that disclaimer.

Mr. WAXMAN. You do have that disclaimer?

Mr. LEVITT. That's up there. The question that has been raised is whether or not that—that disclaimer automatically comes up when consumers, you know, go into the data base or it is somehow at the beginning somehow, so we can look at that. But the disclaimer is there.

Mr. WAXMAN. Does the disclaimer say something like there is no certainty that a reported adverse event can be attributed to a particular product or ingredient? The available information may not be complete enough to make this determination?

Mr. LEVITT. Yes, that's correct.

Mr. WAXMAN. That's your disclaimer?

Mr. LEVITT. Right. And that's up there and that's available, and there are a half dozen other disclaimers along with it.

Mr. WAXMAN. Look, in the ideal world we want you to get to the bottom of the information, put on the website information that's useful for consumers to know but that's accurate. I think that's asking a lot of you because you don't have the staff resources—I know from my experience when I was chairman of the Health and Environment Subcommittee that oversaw legislatively and otherwise FDA. But maybe we should talk further about this issue because it seems to me again that we want the information, even if it is not complete and accurate and full information, to be available to people. We want full disclaimers of that information.

We want you to clean up that website as quickly as possible, and if we are going to ask you to do that then we ought to provide you the funds to do it, among all the other things we want you to do.

Mr. LEVITT. Thank you for recognizing that.

Mr. BURTON. You will find this interesting, but Henry and I agree on this.

Let me just say that it seems to me that it would not be a great deal of additional work, for instance on the Slim Fast issue, which I used earlier. You have got four pages of allegations related to Slim Fast that scared me to death when I read it. I thought, my gosh, I must be missing something because I haven't had any migraines or kidney infections or gall stones or dizziness. So if you could just put out at the side of each one of these allegations, or whatever you want to call them, please see disclaimer, please see explanation at the beginning of the website or something so that people can realize that this might be an isolated case that might be related to something else that they were taking at the same time, I think that would really be helpful.

It shouldn't take a lot of additional work just to put that asterisk out there or some kind of a notation to see the disclaimer.

Mr. LEVITT. We will look into that straightaway.

Mr. BURTON. OK. I want to get back to the issue of companies that are listed on your website as having an adverse event. A lot of times those reports come from doctors, as I understand it.

Mr. LEVITT. Uh-huh.

Mr. BURTON. The companies that may be the subject of the criticism, or adverse event, don't even know about them. They file a Freedom of Information Act request after they find out about them, and they have to wait for a year many times before they really know what the problem is; and that can cause, as I said before, a lot of economic problems as well as other problems.

They have complained to us about that because they have to wait because of the Freedom of Information Act requirements.

Now, did I understand you to say that you have an avenue, other than the Freedom of Information Act, to get that information to these companies so that they can work with you to clear up a problem if it does exist?

Mr. LEVITT. No. I was—you did not understand exactly what I meant to say anyway. What I meant to say was what we need to do—and I said I have allocated some funds to get this done but we are still behind, so that those reports, when they come in are promptly made so they can be made publicly available to the public at large but also certainly to the manufacturer. It is the same preparation process we have to go through, because somebody has to go through every page of the records and be sure that any individual names are not on there.

Mr. BURTON. No, I understand that. But a number of the companies that have contacted us have said, yes, we would like to work with the FDA if these kinds of complaints are made.

Mr. LEVITT. Right.

Mr. BURTON. We would like to get on with it as quickly as possible and clear it up if there is a problem, but because of the Freedom of Information Act and because it takes so long we can't and it does cause problems.

So if there is some way to streamline that, I think it would be helpful to the companies and make people look with a different attitude toward you and the FDA.

Mr. LEVITT. OK. Well, thank you. What we tried to do was to have people on staff do it "when they had time." And what happened was they never had time. So we did take that suggestion and said, all right, we will hire an outside contractor.

We are in the process of training that contractor and being sure that there is somebody dedicated to that task. As I said, it will take us some time to catch up; but, you know, we need to find and have the resources so that is available, because, I mean, the industry complaints, as Mr. Waxman said on this, are correct. They need to have the information, too, and they need to be part of the solution here.

Mr. BURTON. If you could give us some kind of a report after you get this contractor trained and up to speed on how long a company can anticipate having to wait, it would be helpful to just give a general idea, we would sure appreciate that.

Mr. LEVITT. OK. We would be happy to do that.

Mr. BURTON. We discussed the fact that there were some fly-by-night companies making some dangerous products containing ephedra. The number of milligrams that were in the product were excessive, and I think we are going to probably hear from one of the parents who lost their son or daughter because of that.

What did the FDA do when they found out about that?

Mr. LEVITT. Well, I mean, FDA had a really massive effort trying to deal with all of the reports and questions that came in about ephedra.

Mr. BURTON. OK. But when you found out that there was a company that was loading up products with ephedra so that kids could get an artificial high or whatever, it happened to be way above the

norm, did you move and were you successful in getting those products off the market?

Mr. LEVITT. That was a little before my time so I am going to let Dr. Yetley try to answer that question.

Mr. BURTON. Did you get them off the market?

Dr. YETLEY. I assume you are referring to the so-called street drug alternatives.

We did indicate—we put out warning, first of all, so there was public warning, and then we transferred authority—or responsibility for those to our drug center, and they have dealt with those as unauthorized drugs and taken appropriate compliance action.

Mr. BURTON. And they have been removed?

Dr. YETLEY. Yes.

Mr. BURTON. OK. Let me ask you two more quick questions here; and then I would like to, unless another Member has additional questions, hear from the second panel and get back to you.

Mr. WAXMAN. Mr. Chairman.

Mr. BURTON. I am just about finished.

Mr. WAXMAN. Go ahead and finish. I was just going to ask for a unanimous consent.

Mr. BURTON. Sure. Did the legitimate companies that make products, including ephedra, work with you to solve that problem?

Mr. LEVITT. My understanding is there were a number of meetings with representatives from the supplement industry in an effort to try and figure out what can we do to fix this problem. Again, since Dr. Yetley was there, I will let her elaborate if we can.

Mr. BURTON. Can you tell us about the cooperation you received from these companies? Were they cooperative? Were they trying to help to make sure that illegitimate users of ephedra were getting those products off the market?

Dr. YETLEY. We did get good support from the major trade associations, and they did publicly support the agency for dealing with these as drugs.

Mr. BURTON. Did you get that kind of support from the supplement industry as well?

Dr. YETLEY. That's the industry I am referring to, yes.

Mr. BURTON. Thank you very much. I don't have any other questions.

Mr. WAXMAN. Mr. Chairman, is it true that some of these products are still being sold over the Internet? I have one product called X tablets, an herbal Ecstasy alternative. Do you know, in fact, whether some of these products are still available for sale over the Internet?

Mr. LEVITT. Given that, under law, companies make market products without telling the FDA, that is entirely possible. I don't personally have information on it one way or the other. I will ask if anybody else does.

Mr. WAXMAN. I gather there's another place where you are shortchanged in resources and that's the enforcement area.

Mr. LEVITT. Yes.

Mr. WAXMAN. So I shouldn't be surprised if there are products that are being sold?

Mr. LEVITT. It would be entirely possible.

Mr. WAXMAN. I would hope that you would be able to respond to further questions we might have in writing for the record.

Mr. LEVITT. We would be more than happy to.

Mr. WAXMAN. I will ask the chairman for a unanimous consent at the appropriate time so that we can include those in the record.

Mr. HORN [presiding]. Well, without objection.

Mr. WAXMAN. You are the chairman?

Mr. HORN. I am the chairman.

Mr. WAXMAN. Thank you, Mr. Chairman.

Mr. HORN. Without objection, they will be put at this point in the record. Go ahead if you would like to continue questioning.

Mr. WAXMAN. No, no. I want the ability to ask them questions to respond for the record after the hearing.

Mr. HORN. Right. If you want some more time, why, take it.

Mr. WAXMAN. No.

Mr. HORN. Let me ask just a few closing questions here. In reviewing the adverse events website for dietary supplement, it appears that there hasn't been an update since October 1998. Now, that's 7 to 8 months ago. I am just curious, how frequently is the website updated?

Mr. LEVITT. OK. Again, this really is a resource-dependent issue, and what we have tried to do is to focus our attention first on, if you will, the substantive review of the reports and to do the public availability afterwards. In retrospect, we may have gone too far in one direction on that.

We update it, I think, as available. Is there a specific——

Mr. HORN. Why don't you speak in the microphone.

Mr. LEVITT. OK. The goal had been to update it every quarter, quarterly, but we have not been able to keep up with that.

Mr. HORN. Suppose there is a change in that particular item you picked 2 or 3 months before and there is a correction somewhere in a journal or whatever it is, do you try to include those updates?

Mr. LEVITT. OK. Again, the website, as I tried to explain before, I think, is, greatly misunderstood. It is a line listing of reports submitted to the agency, nothing more.

Mr. HORN. Now those reports come from various doctors?

Mr. LEVITT. They come from doctors. They could come from consumers. They come from companies. They come from poison control centers, from States, from whatever source we receive from anyone.

Mr. HORN. So there is no peer review on this?

Mr. LEVITT. No. These are with any spontaneous reporting system. The idea is that if you, whoever you are, a doctor or consumer, feel that you have seen a problem with something, there should be a place that you can send that to; and then it is the responsibility of the recipients, in this case FDA, to go through and do a more detailed analysis of what that entails.

That goes to a lot of the issues we have talked about earlier; but I guess I just want to repeat it again, the website has a whole series of disclaimers. It is not intended to provide an FDA analysis or validation of the information that was reported. It is simply a line listing. It is like a table of contents, of reports, that have been submitted. So somebody looking at it could get an idea of what kinds of products people are writing in about, the kinds of things they are raising, but by no means would it be proper to reach any

conclusions from that website on, ah, there is a problem with this product. That would be grossly incorrect.

Mr. HORN. One last question. How many adverse effects would you estimate have been filed on dietary supplements in the last 7 months? Do you have any feel for those data?

Mr. LEVITT. It has been running about 500 per year.

Mr. HORN. I see. OK. Thank you very much, Mr. Chairman.

Mr. LEVITT. Thank you.

Mr. BURTON [presiding]. I want to thank you, Mr. Levitt.

Let me say this about that. 500 complaints per year? Do you know how many millions of people take these dietary supplements? I think I take a million myself.

Let me thank you. I really appreciate your testimony. Please stick around for a little bit because we might have another question or two for you. I really appreciate your cooperation. Thank you.

We would like to now hear from a public panel. Dr. William Soller of Consumer Health Care Products Association will discuss elements and effective adverse events monitoring system. Dr. Soller has extensive experience with nonprescription drugs and dietary supplements and will offer viable solutions for the problems that have been identified today.

Dr. Theodore Farber is a pharmacologist and a board-certified toxicologist with FDA and EPA experience. He will review the FDA's handling of ephedra adverse events. He conducted an extensive evaluation of the published adverse events on ephedra.

And Dr. Daniel Mowrey is the president of the American Phytotherapy Research Laboratory. He will present testimony on the use of ephedra throughout its history. He will also discuss the level of scientific research in ephedra and what we know through scientific evaluation on usage, serving size, side effects, and adverse events.

Also Dr. Annette Dickinson of the Council of Responsible Nutrition is joining us again to offer advice on how to develop a good monitoring system.

Mrs. Karen Schlendorf is the mother of a young man who, while on spring break in 1996, took Ultimate Xphoria and died.

Ms. Barbara Michal is the founder of H.E.A.T., Halt Ephedrine Abuse Today, a nonprofit organization whose mission is to increase public awareness about the dangers of ephedrine and its related drugs, and to promote the prevention of abuse of ephedrine and its related drugs.

And Dr. Raymond Woosley, a professor of pharmacology and medicine at Georgetown University, will testify about the importance of good adverse events monitoring.

So let me just ask Dr. Soller, Dr. Farber, Dr. Mowrey, Dr. Dickinson, Mrs. Schlendorf, Mrs. Michal, and Dr. Woosley to please stand because this is important. Please raise your right hands.

[Witnesses sworn.]

Mr. BURTON. Let me start with Dr. Soller, and if you could give us an opening statement we would like to, if it is possible, restrict your opening statements to 5 minutes, and then we will get into questions.

I want to apologize for not having more of our members here, but as I expressed before we started, we had some problems here at the beginning of the day and some of the Members are still in that conference and others probably have departed. Please proceed.

STATEMENTS OF R. WILLIAM SOLLER, PH.D., SENIOR VICE PRESIDENT AND DIRECTOR OF SCIENTIFIC AND TECHNICAL AFFAIRS, CONSUMER HEALTH CARE PRODUCTS ASSOCIATION; THEODORE M. FARBER, PH.D., PRINCIPAL, TOXACHEMICA, INTERNATIONAL; DANIEL B. MOWREY, PH.D., PRESIDENT, AMERICAN PHYTOTHERAPY RESEARCH LABORATORY; ANNETTE DICKINSON, PH.D., VICE PRESIDENT FOR SCIENTIFIC AND REGULATORY AFFAIRS, COUNCIL FOR RESPONSIBLE NUTRITION; KAREN SCHLENDORF; BARBARA MICHAL, H.E.A.T.; AND RAYMOND WOOSLEY, PH.D., PROFESSOR OF PHARMACOLOGY AND MEDICINE, GEORGETOWN UNIVERSITY

Mr. SOLLER. Thank you. Good afternoon. I am Dr. Bill Soller, senior vice president and director of science and technology for the Consumer Health Care Products Association [CHPA].

Thank you, Mr. Chairman, members of the committee, for the opportunity to address you on a matter of fundamental importance to the dietary supplement industry, adverse experience reporting.

Founded in 1881, CHPA represents producers of quality nonprescription medicines and dietary supplements, including over 200 member companies across the manufacturing, distribution, supply and service sectors of the self-care industry.

I have had 20 years' experience in the self-care industry, having held scientific regulatory and product development executive positions in consumer health care product companies manufacturing both OTC medicines and dietary supplements and have been with the association since 1985, holding similar responsibilities.

On many occasions in my career, I have personally compiled, analyzed, and reported AERs to FDA on self-care products.

By way of background, let's keep in mind that the vast majority of dietary supplements have a very wide margin of safety. Let's also not forget that there is general agreement that the current sourcing mechanisms for AERs, FDA's MedWatch, SN/AEMS, the consumer hotlines, as well as mechanisms that are maintained by the Consumer Product Safety Commission, U.S. Pharmacopeia, the American Association of Poison Control Centers, the National Institute of Drug Abuse and Centers for Disease Control are adequate signal generators of potential problems with consumer products, though systems integration is needed.

And let's not also forget the bigger picture. Ephedra may be the example today, but we must all take a direct interest in ensuring that in the future the right infrastructure and policies are in place at CFSAN to enable it to handle efficiently, expeditiously, and fairly any and all AERs on dietary supplements.

Therefore, we recommend the following.

As part of Dr. Jane Henney's initial directives as FDA Commissioner, FDA studied prescription drug approvals pre- and post-PDUFA, issuing a report just this month, which calls for an overhaul of the prescription drug AER program, including adoption of

a systems approach to FDA's management of AERs. We support this total quality management approach for CFSAN as well.

Second, we support renewed emphasis within CFSAN on FDA's long-standing overarching safety policy. The policy states for warnings that they must be scientifically documented, clinically significant, and important to the safe and effective use of the product by the consumer. And the significant importance of this policy is that it focuses us on scientific documentation.

Without rigorous critical evaluation of how AER data are collected, analyzed and reported, it is literally impossible to determine their significance.

Third, the controversy surrounding ephedra is clouded by the nature of the data collection and analysis by the agency. This is not unexpected, especially where AERs may be difficult to interpret due to their nature, severity, source, and affected organ systems.

In controversial situations, a refined, integrated system with documented policies and procedures is vital to help ensure that the details of such situations are as accurately documented and professionally handled as possible.

Therefore, we could then concentrate on the science, not the administration, of the process.

In summary then, we recommend that CFSAN prepare a written plan for and adopt a systems approach to managing AERs on dietary supplements, grounded in its current safety policy.

CFSAN should keep current written protocols for CFSAN personnel handling AERs to expedite accurate data collection, including a detailed decision tree for use by those whose responsibility it is to filter serious and nonserious reports and route those reports for expeditious followup.

Third, CFSAN needs a policy and procedures for timely sharing of serious AERs with affected companies in order to help facilitate adequate followup and so address incompleteness and inaccuracies in AER reports. Affected companies are inherently motivated to ensure complete, accurate information on AERs.

Four, specific CFSAN training manuals and procedures should be established to ensure quality collection, analysis, and reporting of AERs.

Five, CFSAN should undertake a review of the core competency of the personnel who would operate different facets of an adequate AER system on dietary supplements.

Six, a reengineering of the public process to AER reports for dietary supplements is needed. AERs should be available to the public in a timely fashion when, A, FDA has communicated with the affected company identified in the AER and; B, is prepared to provide publicly a complete file of the report omitting confidential information, not just a table of contents.

Seven, public input is needed in the development of policies and procedures to be used in CFSAN's systems approach to AER management.

And the time is right for these steps. We want consumers to use safe and beneficial dietary supplements for health promotion and health maintenance. Consumer confidence in these products is essential to their usage, and recognizing that the vast majority of dietary supplements are safe and beneficial, a strong systems ap-

proach to AER management for dietary supplements is nevertheless needed to ensure that those few dietary supplements that may have safety questions are fairly and expeditiously addressed in order to help maintain consumer confidence.

Hence, we urge this committee to take an interest in the recommendations we have set forth concerning CFSAN's management of AERs for dietary supplements.

We are pleased to hear that Mr. Levitt would use the $2.5 million budget request to upgrade CFSAN's AER system. However, we recommend that the committee consider a specific inquiry to FDA asking for a detailed resource allocation plan for adopting a documented systems approach to AER management.

Thank you, Mr. Chairman, members of the committee.

Mr. BURTON. We would like to have your requests and recommendations in writing, if you have those, and we will look at them ourselves and also submit them to Mr. Levitt and to FDA.

Mr. SOLLER. Yes, sir. We provided them prior to the meeting to counsel.

Mr. BURTON. OK. Fine. Thank you. I haven't had a chance to read them yet, but I will.

[The prepared statement of Mr. Soller follows:]

Producers of Quality Nonprescription Medicines and Dietary Supplements for Self-Care

CONSUMER HEALTHCARE PRODUCTS ASSOCIATION
Formerly Nonprescription Drug Manufacturers Association

Statement of the Consumer Healthcare Products Association

Submitted by R. William Soller, Ph.D.
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Committee on Government Reform
Congress of the United States House of Representatives
Hearing on
Dietary Supplements and Adverse Experience Reporting
Thursday, May 27, 1999
2154 Rayburn Office Building
Washington, D.C.

Good afternoon. I am Dr. Bill Soller – Senior Vice President and Director of Science & Technology for the Consumer Healthcare Products Association (CHPA). Founded in 1881, CHPA represents producers of quality nonprescription medicines and dietary supplements, including over 200 member companies across the manufacturing, distribution, supply and service sectors of the self-care industry.

Thank you, Mr. Chairman and members of the Committee, for the opportunity to address you on a matter of fundamental importance to the dietary supplement field – adverse experience reporting (AER). Our comments on adverse experience reporting for dietary supplements focus on three basic points:

- Adoption of a systems approach to AER, including establishment of the appropriate infrastructure for continuous quality management of adverse event reports (AERs) on dietary supplements.

- Continued application, with renewed emphasis, of the Food and Drug Administration's (FDA) long-standing, overarching safety policy for foods and drugs.

- Adoption of appropriate procedures for operations and training pertaining to AER management for dietary supplements.

In the course of elaborating on these points, I will comment on several examples where systems improvement would help advance the field.

I. Introduction

By way of introduction, it is important to keep in mind three important observations about today's dietary supplement field.

First, the vast majority of dietary supplements have a very wide margin of safety. Products such as garlic, ginko biloba, ginger, St. John's wort, saw palmetto, calcium, fat-soluble vitamins A, D, E, and K, thiamine, riboflavin, vitamin C, bioflavenoids, and many others have well characterized use profiles spanning, in many cases, hundreds of years of use.

That is not to say that we should not be on guard, for example, for rare interactions between foods, such as dietary supplements, and new chemical entities approved as prescription drugs. We need a continuously improving AER system for consumer products, both drugs and foods. However, because of the inherent safety of the vast majority of dietary supplements, one could reasonably project a lower resource need and fewer personnel within FDA to effectively manage AERs for dietary supplements than for drugs.

Second, FDA has at least three systems in place for capturing adverse experience reports[1] on dietary supplements:

- MedWatch, which is the FDA's program for health professionals to report serious reactions and problems with medical products such as drugs and medical devices; consumers may also use the MedWatch system to report medical problems with products directly to their health professionals or FDA (e.g., via mail or internet);
- Special Nutritional Adverse Event Monitoring System (SN/AEMS), which was established in early 1993 following the establishment of the Office of Special Nutritionals as a means to compile and report AERs relating to dietary supplements and receives AERs from a variety of sources besides FDA's MedWatch program, including FDA's field offices, other federal, state, and local public health agencies, letters and phone calls from consumers and health professionals, and which directs consumers and health professionals to the MedWatch homepage for reporting purposes.
- Consumer Hotline numbers to FDA (e.g., MEDWATCH 1-800-332-1088; FDA Consumer Hotline: 800-532-4440; CFSAN Information Line: 1-800-FDA-4010).

The current mechanisms of capturing AERs[2] are similar to those used for drugs, and are adequate to create signals as to potential ingredient safety problems. Typically, the nature of the signal is

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[1] There are certain caveats concerning the use of adverse experience reports provided spontaneously to FDA. As noted on the CFSAN's SN/AEMS homepage:
- There is no certainty that a reported adverse event can be attributed to a particular product or ingredient. The available information may not be complete enough to make this determination.
- The total number of adverse events cannot be used to estimate the rate of occurrence in the population. Not all adverse events are reported, and there are no reliable data on population use patterns.
- Reporting of an adverse event may be affected by many factors, including length of time a product or ingredient has been marketed or publicity.
- Comparisons of the safety of one product vs. another cannot be directly obtained from these data; available information may not be complete enough to make this comparison.
- The inclusion of a product as a special nutritional in the SN/AEMS does NOT necessarily represent its legal/regulatory status. The available information may not be complete enough to make this determination.

[2] In addition, the Consumer Product Safety Commission manages the National Electronic Injury Surveillance System (NEISS), which is a probability sample of hospital emergency rooms in the United States that is used by the CPSC to measure the magnitude of the injury problem associated with consumer products and to provide a source for follow-up investigations of selected cases. The Substance Abuse and Mental Health Services Administration conducts a

clearest when the outcome of exposure to an ingredient is sufficiently well characterized to suggest causality, such as in the case of pediatric accidental ingestions associated with iron-containing dietary supplements[3] or choking associated with water soluble gums (i.e., guar gum, karaya gum, plantago seed (psyllium), tragacanth, and xanthan gum) due to inadequate concomitant water intake during dosing[4]. In these cases, for example, relatively few AERs may be sufficient to lead to changes in labeling and/or packaging. In other cases, where the reported nature of the putative exposure outcome is ambiguous, due to the potential for concomitant ingredient/toxin exposure or to concurrent underlying condition(s)/disease(s), the matter is not so straightforward, requiring a much more comprehensive analytical approach. In either case, there is general agreement that current sourcing mechanisms for AERs from consumer products are adequate as gross signal generators of potential problems. This is not to be confused, however, with the need for refinements in the systems management, analytical policies, and operational policies and procedures for handling AERS reportedly associated with dietary supplements obtained from these sources, as detailed below.

Third, while CHPA is not necessarily defending any one ingredient or constituent in its comments, we are aware that there have been significant concerns expressed about the method of collecting and analyzing ephedra-related AERs. Because of the importance of adequate adverse experience reporting on all consumer products, we take a direct interest in ensuring that the infrastructure and policies are in place at FDA to handle efficiently, expeditiously, and fairly any and all AERs on dietary supplements in the future.

II. Adoption of a Systems Approach to FDA's AER Management

As part of her initial directives as FDA Commissioner, Dr. Jane Henney established a task force that prepared a white paper on "Managing the Risks from Medical Product Use: Creating a Risk

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similar survey (Drug Abuse Warning Network-DAWN) for drug-related health problems. The American Association of Poison Control Centers also manages the Toxic Exposure Surveillance System (TESS) which collects reports on chemicals, drugs and other consumer products to Poison Control Centers in the test reporting network.

[3] Iron-Containing Supplements and Drugs; Label Warning Statements and Unit-Dose Packaging Requirements [59 F.R. 51030-51058 (10/6/94)]

[4] Warning Statements Required for Over-the-Counter Drugs Containing Water-Soluble Gums as Active Ingredients; Notice of Proposed Rulemaking [55 F.R. 45782-85 (10/20/90)]

Management Framework."[5] This white paper focuses mainly on the Center for Drug Evaluation and Research (CDER) and FDA-approved medical products. While supporting the fact that user fees and recent new efficiencies in the new drug review process have not resulted in the approval of products with substandard safety profiles, the report calls for adoption of a systems approach to FDA's management of AERs including each Center establishing "separate quality assurance/quality control units," ensuring and documenting "ongoing professional education and core competency training for all reviewers," maintaining current "good review practice documents," ensuring rapid completion of AERs, and integrating "existing post-marketing systems so analytical tools, data entry, and editing can be uniformly applied, and information is readily available to all reviewers."

In common parlance, the white paper urges a TQM – or total quality management -- approach to AER collection, analysis, review and reporting with appropriate self-improving feedback loops to ensure continuous quality assessments and improvements.

We support this type of approach for all FDA Centers and specifically for AER management by the Center for Food Safety and Applied Nutrition (CFSAN). Components of such an approach must involve the development of appropriate guiding policies and procedures and receive adequate funding.

III. Continued Application, with Renewed Emphasis, of FDA's Long-standing, Overarching Safety Policy for Foods and Drugs.

FDA has a long-standing, overarching safety policy for evaluating risks reportedly associated with foods and drugs. The policy states:

> "Warnings shall be scientifically documented, clinically significant and important to the safe and effective use of the product by the consumer."[6]

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[5] U.S. Health and Human Services, Food and Drug Administration Task Force on Risk Management: Managing the Risks from Medical Product Use; Creating a Risk Management Framework, May 1999.

[6] See *Federal Register* 47: 54754, 1982 (for a detailed discussion of this policy, see: Soller, R.W., When to Warn, *Regulatory Focus*, Volume 2 Issue 10 October, 1997).

With the escalating consumer demand for, and exposure to, dietary supplements, CFSAN should place renewed emphasis on this policy to help ensure AER reviewers are appropriately grounded before undertaking risk-analysis of AERs reportedly associated with dietary supplements

The first step articulated by this policy -- i.e., scientific documentation – is by far the most critical. Without rigorous, critical evaluation of how data are collected, analyzed and reported, it is literally impossible to determine their significance in a controlled clinical setting or in the general population of consumers. Renewed emphasis on this long-standing policy would help inform all stakeholders as to the basic ground rules for making regulatory decisions on the safety of dietary supplements. Importantly, FDA's long-standing policy is consistent with a systems approach to AER management.

IV. Adoption of Appropriate Procedures for Operations and Training

We support the development of specific operational policies for the Special Nutritional Adverse Event Monitoring System. Further, we also support the development of specific training manuals and protocols for use by CFSAN personnel in managing AERs for dietary supplements.

The controversy surrounding, for example, ephedra, is clouded by questions about the nature of data collection and analysis by the Agency. This is not at all an unexpected situation where AERs by their nature may be open to different interpretations. Often, there are uncertainties as to documentation of the details of AERs. In some situations, such as the recent enforcement action against GBL-containing products and the regulatory resolution of labeling and packaging changes for iron-containing dietary supplements, there appear to have been relatively straightforward sets of circumstances and consequences associated with use as recommended (i.e., GBL) or use in overdose (i.e., iron). AERs reportedly associated with ephedra, however, appear less clear, by virtue of their reported nature, affected organ system, severity, and source. It is in situations such as this where refined systems are needed to help ensure the controversial situations are as accurately documented and professionally handled as possible.

Such operational refinements include appropriate policies and procedures for a system of continuous quality management of AERs on dietary supplements, which are available for public review, including for example:

- A written plan for integrating an overall quality management systems approach for adverse experience reporting on dietary supplements;
- Written protocols for CFSAN personnel handling AERs on dietary supplements to expedite accurate data collection, including a defined algorithm (i.e., decision tree) for use by FDA personnel whose responsibility is to filter serious and non-serious reports and route these reports for expeditious follow-up;
- A policy and procedure for timely sharing of serious AERs reported to FDA with affected companies to facilitate adequate follow up to address incompleteness and inaccuracies, affected companies are inherently motivated to ensure complete, accurate information in AERs, thereby being a potential resource partner for FDA);
- Specific training manuals and procedures to ensure quality collection, analysis and reporting of AERs on dietary supplements;
- A review of the core competency of the personnel needed to operate different facets of an adequate AER system on dietary supplements;
- A re-engineering of the public access to AER reports for dietary supplements, so that incomplete and potentially misleading listings of poorly substantiated AERs are not made publicly available (e.g., on SN/AEMS). AERs should be available to the public in a timely fashion when FDA has communicated with affected companies identified in the AER and is prepared to provide a complete report file omitting confidential information;
- Public input to the development of the manuals of policies and procedures to be used in a systems approach to AER management for dietary supplements.

V. Summary

FDA has scheduled Stakeholder meetings for June 8 and July 20 to assist in the development of an overall strategy for dietary supplements.

We support this and note that AERs are among the elements of an overall strategy that CFSAN seeks to address. We also note that FDA sought $2.5 million in its budget for post-marketing surveillance activities on all foods, with an unspecified amount earmarked for dietary supplements.

We recommend that the Committee consider a specific inquiry to FDA, asking for the detailed allocation plan for these resources, including a review as to whether CFSAN plans to: adopt a risk management systems approach to the handling of AERs reportedly associated with dietary supplements; place renewed emphasis on the agency's long-standing, overarching scientific policy on managing AER reviews; and adopt specific operational policies and procedures for AER management and training.

The time is right for these steps to be undertaken by CFSAN. It is sound public policy to encourage consumers to use safe and beneficial dietary supplements for promoting and maintaining health. Consumers must have confidence in the products they use. Recognizing that the vast majority of dietary supplements are safe and beneficial, a strong systems approach to AER management for dietary supplements is needed to ensure that safety questions are fairly and expeditiously addressed. Hence, we urge this Committee to take an interest in the recommendations we set forth for CFSAN's management of AERs on dietary supplements.

NEWS RELEASE

CONSUMER HEALTHCARE PRODUCTS ASSOCIATION
Formerly Nonprescription Drug Manufacturers Association

Embargoed For Release
May 27, 1999

Contact: Donna Edenhart
(202) 429-9260

CHPA Tells Congress the Time is Right for Adverse Experience Reporting Systems on Dietary Supplements

Washington, D.C. – The Consumer Healthcare Products Association (CHPA) recommended today that the Food and Drug Administration (FDA) refine its systems for monitoring the safety of dietary supplements. In testimony presented to the House of Representatives Committee on Government Reform, CHPA asked the Committee to consider several recommendations for FDA's management of adverse experience reporting (AER) for dietary supplements.

FDA already has a safety policy in place that evaluates potential safety risks that may be associated with both foods and drugs. The Government Reform Committee held the May 27 oversight hearing in light of increased usage of dietary supplements in the United States and the need to further improve the existing reporting system to monitor rare, serious, adverse events.

In its comments, CHPA stated that it is sound public policy to encourage consumers to use safe and beneficial dietary supplements for health promotion and health maintenance. The Association also reminded the Committee that while the vast majority of dietary supplements are safe, the possibility of rare interactions between foods, such as dietary supplements and newly approved prescription drugs, necessitates a continuously improving AER system.

CHPA recommended that the existing AER system should be further improved by using three basic methodologies, including: a systems approach to AERs for continuous quality management; continued application, with renewed emphasis, of FDA's longstanding safety policy for foods and drugs; and appropriate procedures for operations and training for AER management.

(continued)

CHPA acknowledged that FDA currently has at least three programs in place for collecting AERs on dietary supplements which are adequate to identify potential ingredient safety problems -- MedWatch, the Special Nutritional Adverse Event Monitoring System (SN/AEMS) and consumer telephone hotline numbers. However, CHPA stressed that there is still the additional need for refinements in the systems management, analytical policies and operational policies and procedures for handling dietary supplement AERs gathered from those sources.

CHPA concluded its comments by offering support for FDA's June 8 and July 20 Stakeholder meetings which have been scheduled to prepare an overall strategy for dietary supplements. The Association pointed out that since AERs will be discussed at the meetings, the time is right for FDA to take the necessary steps to ensure that those dietary supplements with safety questions are fairly and expeditiously addressed, in order to advance the overall dietary supplement field and maintain consumer confidence.

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CHPA, formerly the Nonprescription Drug Manufacturers Association (NDMA), is the 118-year-old national trade association representing U.S. manufacturers and distributors of nonprescription, over-the-counter (OTC) medicines and dietary supplement products.

CHPA Web Site: www.chpa-info.org

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Mr. BURTON. Dr. Farber.

Mr. FARBER. Thank you, Mr. Chairman.

I am Dr. Theodore Farber. I am——

Mr. BURTON. Can we get you to pull the mic a little closer?

Mr. FARBER. Sure.

Mr. BURTON. Thank you.

Mr. FARBER. I am Dr. Theodore Farber. I am president of ToxaChemica, International, which is a consulting toxicology firm located in Rockville, MD.

Before founding this company, I was in government service at the Food and Drug Administration for over 19 years, serving in many senior science positions.

I then served 4 additional years at the Environmental Protection Agency, as a member of the Senior Executive Service. I was director of the health effects division in the pesticide program at EPA and supervised and developed the science policy for the largest group of regulatory toxicologists in the world.

I am board certified in toxicology for the last 20 years, and I believe I enjoy an international reputation in my discipline.

Mr. Chairman, if there is only one thing that I could say to the committee, it would be that I have looked at every report in the Food and Drug's AER reporting system in the docket, and I can confirm my belief that dietary supplements containing ephedra, when used according to the label, are safe and effective and have been used for millions of people here in America.

Food and Drug's current system does not provide valid information to the FDA, the public, and the industry about safety of dietary supplements. Instead, because of the way in which AERs are currently handled at Food and Drug, the AER lacks standardized methodology, and this leads to inconsistent applied science from one case to the other.

It causes public confusion over whether an adverse effect was professionally assessed and actually connected with the product mentioned and whether it is simply mentioned as one of the many potential causes, including preexisting conditions and natural causes in other products that may have caused or produced a negative reaction; and it is wasteful of the agency's resources to pursue whole categories of products, branding them as unsafe when the agency might better focus its attention on specific products that are irresponsibly manufactured and marketed.

This is a summary of how Food and Drug's AER system works. Reports from any source concerning the dietary supplement product are received by Food and Drug. They are collected and filed within this AER system. The vast majority of reports, particularly for any product that is the subject of an FDA press release, comes to Food and Drug through a hotline, a number that Food and Drug publicizes. These reports are, almost without exception, anecdotal reports from lay persons who heard about or allege to have had an experience, an adverse effect.

These reports are useless from a scientific perspective, as they typically lack one or more pieces of information critical to scientific analysis, including product identity and ingredients, product dose, frequency and duration, and medical records describing the adverse effects in accurate medical terms.

FDA's system does not take into account whether or how publicity affects the reporting rate and I have with me—and it is in my written testimony—charts showing that most of the reports FDA has received were as a result of FDA press releases and followup TV programs stating that ephedrine products are dangerous and have killed people. These press releases and TV shows encourage the public to call an FDA hotline to report any problems.

I would like to make one final point. The AER files supporting this proposed rule were in such a disarray when the rule was first published that Food and Drug was required to take unprecedented steps of closing the rulemaking to fix the AER files. Even after this process was completed, I found that the vast majority of AERs for these products, almost 85 percent of these events FDA had publicized as associated with ephedra products, were informationally worthless.

Further, FDA has placed in the docket for that proposed rule a clear statement of its policy on AERs, which acknowledges the scientific fact that unevaluated AERs are inherently unreliable and, therefore, should not be used to establish product risk.

Nonetheless, as Food and Drug has implicitly stated in black and white in the proposed rule, FDA relied on just 13 AERs to establish proposed serving limits for these products, which conservative estimates show that there have been billions of these servings sold that have been consumed by millions of consumers.

FDA even admitted in writing in the proposed rule that the agency had not scientifically evaluated these 13 AERs to determine whether there was any connection to product consumption in the 13 reported events. In fact, the treating physician in 1 of the 13 cases stated that there was no such connection.

Therefore, Food and Drug was almost forced to admit in writing in the proposed rule that the agency's proposed serving limits may have no public health benefit.

Mr. Chairman and members of the committee, I thank you for the opportunity to address you today, and I would be more than happy to answer any questions.

Mr. BURTON. Thank you, Dr. Farber.

[The prepared statement of Mr. Farber follows:]

Statement of Theodore M. Farber

Submitted by Theodore M. Farber, Ph.D., DABT
President
ToxaChemica, International
Rockville, Maryland

Committee on Government Reform
Congress of the United States
House of Representatives

Hearing on
Dietary Supplements and Adverse Experience Reporting
Thursday, May 27, 1999
2154 Rayburn Office Building
Washington, D.C.

I am Theodore M. Farber, the president of Toxachemica International, a toxicology consulting firm located in Rockville, Md.

Before founding this company I was in government service at the Food and Drug Administration for over nineteen years, serving in several senior science positions. I then served four additional years at the Environmental Protection Agency. As a member of the senior executive service, I was director of the Health Effects Division in the pesticide program at EPA and supervised and developed science policy for the largest group of regulatory toxicologists in the world. I have been board-certified in toxicology for the last twenty years and I believe I enjoy an international reputation in my discipline.

I have been asked to testify today because of my expertise in food safety and my familiarity with FDA's current system for handling adverse event reports for dietary supplements, which I will refer to as FDA's AER system. I understand that others here today will testify as to the remedy for the problems with FDA's current system. However, before a remedy is found, it is necessary to know how the system is broken.

It is my professional view that FDA's current system does not perform its intended function – that is, the system does not provide valid information to FDA, the public and industry about the safety of dietary supplements. Instead, because of the way in which AERs are currently handled at FDA, the AER system's lack of standardized methodology leads to:

1. inconsistently applied science from one case to another;

2. public confusion over whether an adverse report was professionally assessed and actually connected to the product mentioned, or whether it was simply mentioned as one of many potential causes, including preexisting conditions, natural causes, or other products, that might have produced a negative reaction; and

3. wasteful expenditure of agency resources to pursue whole categories of products and branding them as unsafe, when the agency might better focus its attention on specific products that are irresponsibly manufactured and marketed.

Without standard scientific methods, a serious adverse event in one case might result in agency over-reaction, whereas in another case the agency may determine that even more serious adverse events are in the acceptable, or expected, range of risks.

Very briefly, this is a summary of how FDA's AER system currently works. Reports from any source concerning a dietary supplement product that are received by FDA are collected and filed within the AER system. The vast majority of reports, particularly for any product that is the subject of FDA press releases, come to FDA through a hotline number that FDA publicizes. These reports are almost without exception anecdotal

reports from laypersons, often from friends or relatives of the person alleged to have experienced an adverse effect. These reports, because FDA does not have the resources to perform the necessary followup, are useless from a scientific perspective as they typically lack one or more pieces of information critical to scientific analysis, including product identity and ingredients, product dose and duration, and medical records describing the adverse event in accurate medical terms.

Further, FDA's system, since there is little or no analysis of AERs the agency receives, does not take into account whether or how publicity affects the reporting rate. I have with me charts showing that, with respect to ephedra AERs, most of the reports FDA has received were the result of FDA press releases and followup television programs, such as the Montel Williams show, stating that ephedra products are dangerous and have killed people. These press released and TV shows encouraged the public to call an FDA hotline to report any problems. The charts show that FDA received huge numbers of reports in connection with such publicity. Had FDA done its own analysis of the AERs, the agency would have recognized the need to do a careful assessment of whether these reports actually had anything to do with ephedra consumption, something the agency admittedly never did.

Notwithstanding that the vast majority of the AERs in FDA's current system are scientifically worthless, and therefore meaningless with respect to the safety of any dietary supplement product, these reports are published on FDA's internet website, and thus made available around the world, as events "associated with" the product and manufacturer identified in the website report. I have here and in the materials attached to my testimony a copy of part of FDA's website. You can see many examples of reports of alleged events for a variety of products. However, there is no way to tell whether the report is meaningful from the website because of the minimal information provided.

This leads me to the final problem with FDA's current system. There is no way to obtain the files from FDA for the website AERs to determine whether they are a real report that FDA, the public and industry should care about, or just some report from a friend of a friend in response to a TV show with the FDA hotline phone number on it. I know this because we have attempted to obtain through multiple Freedom of Information Act Requests the background reports for AERs for ephedra products. Even though FDA has taken the trouble of publishing these reports on the internet, FDA has refused for almost a year to release the background files, which are essential to the question of product safety. FDA's excuse, and it is likely a valid one, is that they are too busy.

FDA obviously needs more resources to do the job right. However, the agency should not be publishing reports on its website that are meaningless, and then refusing to provide the files that are critical to the scientific question of safety to the public. This process scares the public and hurts industry, without any public health benefit. Indeed, the process creates an enormous problem for FDA, for it is difficult to argue with industry"

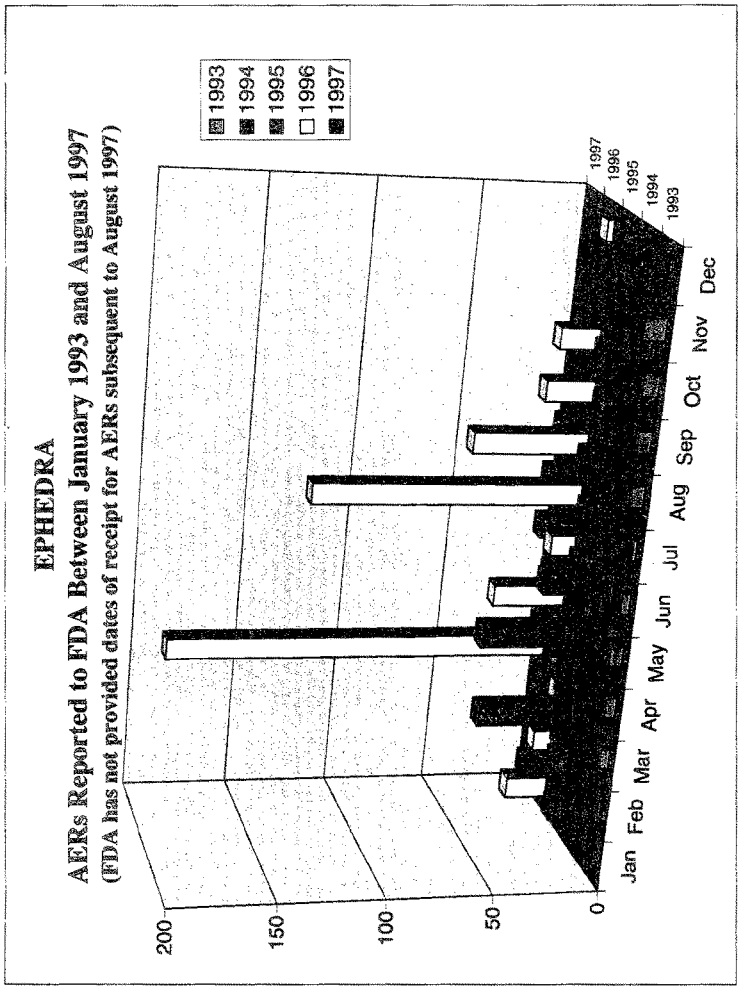
perception that the primary intent of this exercise is to damage the dietary supplement industry.

The Small Business Administration reviewed FDA's ephedra proposal and agreed that the AER system is not a source of useful information. I quote, "In addition to the lack of data in the AER reports, industry experts who carefully reviewed each AER in the docket discovered some astonishingly peculiar and irrelevant information. The experts found cases where adverse events occurred absent the use of an ephedra product, cases where no adverse effect was listed, events medically unrelated to ephedrine ingestion, and other bizarre reports like a case where a patient became pregnant though using an implanted birth control device. These reports have no rational relationship to the safety or efficacy of ephedrine alkaloid products." FDA must find a way to keep irrelevant but damaging information off the internet.

I would like to add one final point. My interest in FDA's AER system stems from my review of FDA's AER files that were used as a basis for the agency's June 1997 proposed rule on supplements containing ephedra. That rule provides some useful examples of how FDA's mishandling of these reports can cause serious problems. The AER files supporting this proposed rule were in such disarray when the rule was first published that FDA was required to take the unprecedented step of closing the rulemaking to fix the AER files. Even after this process was complete, I found that the vast majority of the AERs for these products, almost 85% of the events FDA had publicized as "associated with" ephedra products, were informationally worthless. Further, FDA has placed in the docket for that proposed rule a clear statement of its policy on AERs (a copy is provided with my materials), which acknowledges the scientific fact that unevaluated AERs are inherently unreliable and therefore cannot be used to establish product risk. Nonetheless, as FDA has explicitly stated in the black and white in the proposed rule, FDA relied on just 13 AERs to establish proposed serving limits for these products, which conservative estimates show have had billions of servings sold and have been consumed by millions of consumers. FDA even admitted in writing in the proposed rule that the agency had not scientifically evaluated these 13 AERs to determine whether there was any connection to product consumption and the 13 reported events. The treating physician in one of the 13 case stated that there was no such connection. Therefore, FDA was also forced to admit in writing in the proposed rule that the agency's proposed serving limits may have no public health benefit.

FDA may now disagree with my statements concerning this rule, but the agency's own words published in this 1997 proposed rule establish the facts of this matter.

FDA desperately needs to focus on revising its AER system. Additional resources will be required. The immediate action that FDA should take, which will not require additional resources, is to remove the current AER database from the website until such time as the agency can respond expeditiously to public requests for AER files.


EPHEDRA
AERs Reported to FDA Between January 1993 and August 1997
(FDA has not provided dates of receipt for AERs subsequent to August 1997)
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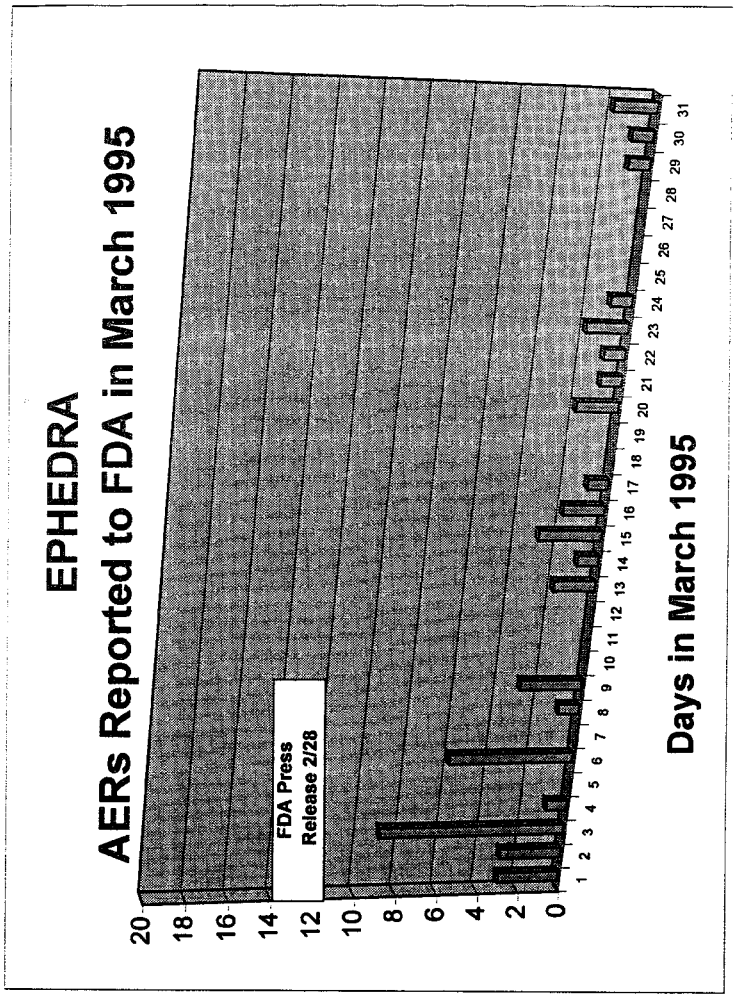
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AERs Reported to FDA in March 1995
FDA Press
Release 2/28
Days in March 1995
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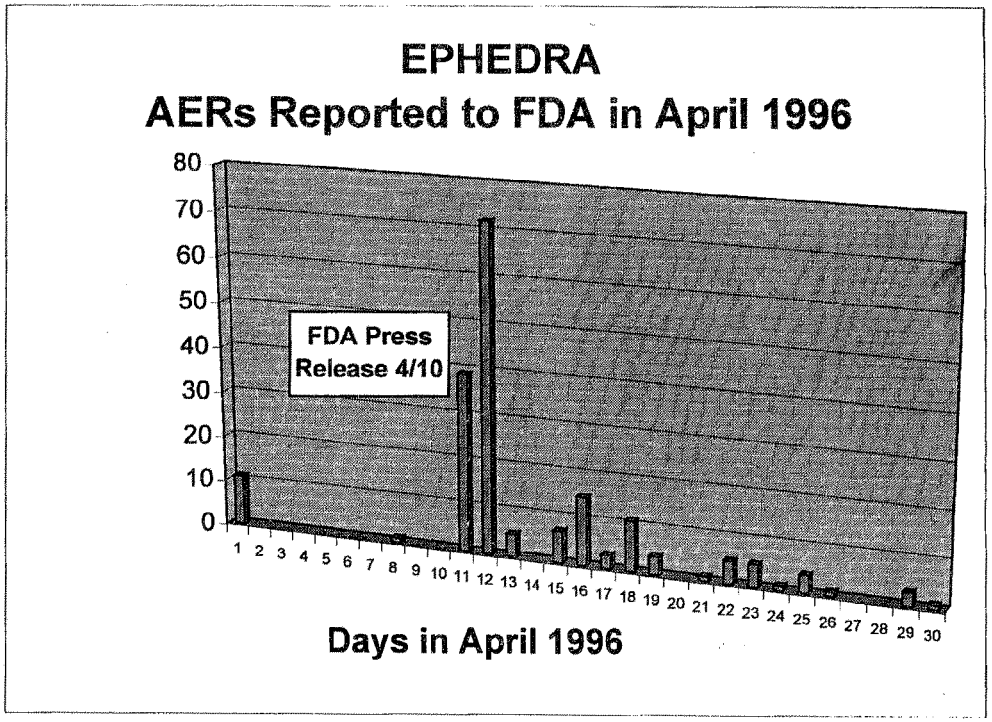
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AERs Reported to FDA in April 1996
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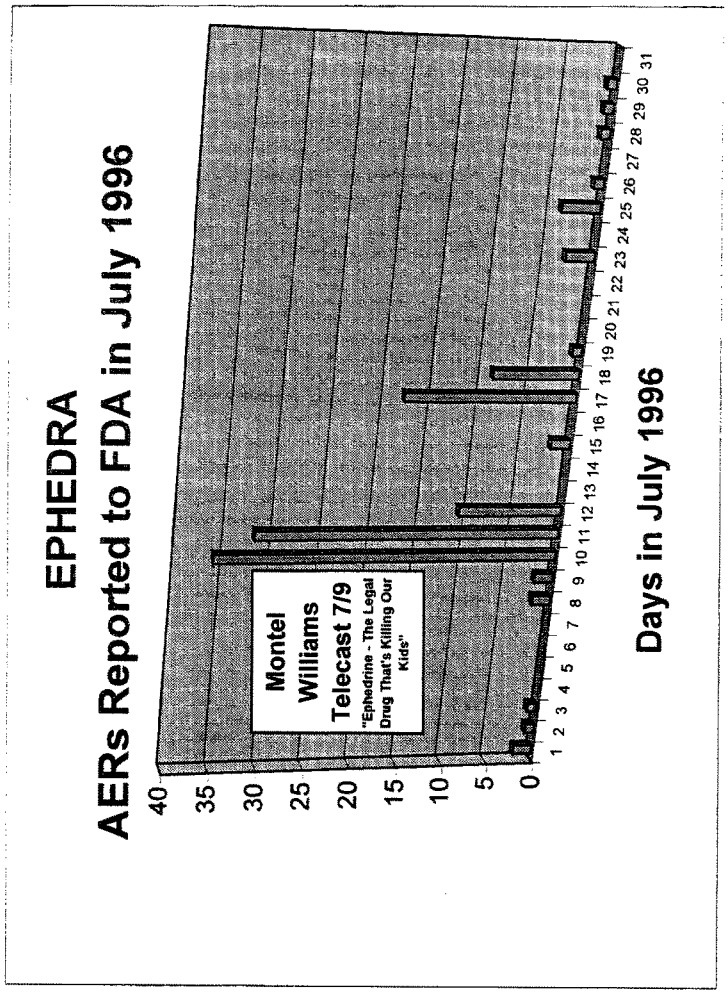
FDA Press Release 4/10
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30
Days in April 1996


EPHEDRA
AERs Reported to FDA in July 1996
Montel Williams Telecast 7/9
"Ephedrine - The Legal Drug That's Killing Our Kids"
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1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31
Days in July 1996

SN/AEMS DISCLAIMERS

The evaluation of data in passive surveillance reporting system that as SN/AEMS is limited by several recognized factors:

Because reporting is voluntary, adverse events may occur which are not reported, and are therefore not in SN/AEMS.

A single case may be reported more than once, inflating the number of reports in the system. Health care professionals are encouraged to report all suspected adverse events. In addition, consumers of these products and other individuals may also report suspected reactions to these products. All confirmed duplicated reports are removed from SN/AEMS.

There is no certainty that an adverse event can be attributed to a particular product, or ingredient in a product.

An event may be related to or modified by an underlying disease or condition, to other products which are taken concurrently, or the event may have occurred by chance at the same time the suspected product was taken.

Accumulated case reports cannot be used to calculate incidence or estimates of product risk. They must be carefully interpreted as reporting rates, and not as occurrence or incidence rates. The length of time that a product has been marketed, the market share, experience and sophistication of the population using the product or evaluation the adverse event, publicity about an adverse reaction, and regulatory actions are all factors that influence the probability that an adverse event will be reported. Comparisons of product safety cannot be directly obtained from these data.

				cellulase, trypsin, lipase, protease, bromelain, raw duodenum
12747	Vomiting blood, bleeding orally and anally, severe headaches	DHEA	Ultra Tech Brand	DHEA
12748	Constant headache	Jevity	Ross Products Division/Abbott Laboratories	Unknown
12749	Heart palpitations	Sinfully Cinnamon Herb Tea	R. C. Bigelow, Inc	cinnamon, rose hips, hibiscus flowers, apples, orange peel, peppermint, ?, licorice root, ?, natural flavor
12750	Fingernails fell off	Neutral C + CoEnzyme Q10	New Vision International	vitamin C, vitamin B6, folic acid, vitamin B12, calcium, magnesium, selenium, potassium, coenzyme Q10, taurine, glycine, L-serine, L-proline, hydroxyproline, citrus bioflavonoids, lysine HCl, PABA, L-methionine
12751	Acid stomach, headache	Yeast Defense	Nutrition Now	Unknown
12752	Tongue swelling, had difficulty swallowing	Echinacea	Unknown	echinacea
12756	Developed jaundice with hepatitis	Chaparral	Unknown	chaparral
12757	Flushing reaction, tingling, and warm feeling	Vitamin C	Tishcon Corporation	vitamin C
12758	Flushing and "hot feeling"	Vitamin C	URL	vitamin C
12759	"Bones ached"	Bone Guard	Spectramin, Inc	calcium, magnesium, horsetail, boron, vitamin D
12760	Chest pains	St. John's Wort	Unknown	St. John's wort
12761	15-year-old with rapid heartbeat, severe cramps, nausea	Unspecified ma-huang product	Unknown	ma-huang

13052	Dull pressure chest pain radiating to neck persisted for a least 3-4 hours	St. John's Wort	Unknown	St. John's wort
13053	Prothrombin time changed	Now St. John's Wort	Now Natural Foods	St. John's wort
13054	Gastrointestinal distress including bloody diarrhea; nervous shakes, blurred vision, and bleeding gums	Equinox Master Liquid Mineral Complex	Equinox International Corp	minerals
13055	Hives	Your Life Calcium Tabs with Vitamin D and Minerals	Delavau, JSW Co, Inc	calcium, vitamin D, minerals
		Vitamin E	Unknown	vitamin E
		Vitamin C	Unknown	vitamin C
13056	Swelling and pain on the right side of the head, right eye, along with a visual field defect	Freeze Dried Echinacea	Eclectic Institute	echinacea
13057	Profuse sweating, warm feverish feeling, eye spasms, constant and frequent, extreme irritability, nervousness, weight gain, exhaustion, falling asleep at odd times and places while driving	Vitasana	Unknown	Unknown
13058	Change in behavior, erratic sleeping patterns and mood swings, showed signs of withdrawal	Metabolift	Unknown	Unknown
13059	"Starry-eyed," unresponsive, unable to ambulate, speechless	Valerian	Wonder Lab	valerian
13061	Cellulitis, hepatitis C	Formula 601	Nutritional Enzyme Support System,	Unknown

Mr. BURTON. Dr. Mowrey.

Dr. MOWREY. Mr. Chairman, members of the committee, thank you for inviting me here today.

My name is Dr. Daniel Mowrey. I own a company called American Phytotherapy Research Laboratory near Salt Lake City, UT, where our main activity is to investigate the medicinal properties of plant materials, their safety and efficacy.

For the past several years, I have been involved in the investigation of ma huang, its perhaps medicinal properties, its health benefits, its historical uses and so forth.

I have authored a book on the subject called Thermogenesis: Fat Management Related. I think you have a copy there. It deals with the historical background relating the advent, if you will, of ma huang and ephedrine into the weight loss category and what scientific support there is for that. I think I list about 1,400 references in there to detail how that has all come about.

I was asked to testify today about the historical use of ephedrine on ma huang. In doing that, I thought it was fairly impossible to know how long people have benefited from ma huang. However, some time ago I read where ephedra plants were found in a grave alongside the remains of a Neanderthal man dating back about 20,000 years.

This seemed like a good starting point to begin a historical discussion of ma huang, but I must admit to some degree of hesitation in citing this ancient case. It might just wind up in some AER. I can see the headlines now, Killer Herb Has Been Killing People for 20,000 Years.

Anyway, back to my point. This case of, this Neanderthal case, I think demonstrates mankind's long association with ma huang. Chinese and other Asian texts show that ma huang has been traditionally used in herbal medicine for at least 5,000 years.

Now, in traditional Chinese medicine, the twigs of this rather scraggly looking ma huang plant were broken up or pulverized and brewed up as a tea. They didn't have capsules in those days, in the ancient days, but they did have a lot of teas.

Several ounces could be used in one serving, and a serving could be taken several times a day. It was served as a tonic; or it was concentrated to be used in the treatment of colds, fevers, and other debilitating conditions.

All in all, I think it was a highly prized herb, used throughout Asia; and it still is to this day, for these traditional systems have not changed much in the way that they use medicinal plants.

By the way, seldom was ma huang used by itself. It was most often combined with a variety of other plants that moderated its effectiveness and its action in the body; and I think that that particular property of ma huang is evident in the way that it is used in modern therapy in weight loss.

Now, although ephedra is normally associated with traditional Chinese medicine, it does grow in the United States, at least related species can be found here. As a matter of fact, early American settlers in Utah, where I reside, brewed up a beverage known as Mormon tea or Brigham tea. It was a favorite beverage and it was used by pioneers to combat exhaustion and fatigue, and often as a

primary source of energy or food, since the conditions in the early pioneer days in Utah were not very good.

Brigham Young was said to enjoy an occasional cup of this namesake tea, although I don't think we have any evidence that any of his 20-some-odd wives did that.

The point to all of this is to show that throughout recorded history, in cultures around the world, ephedra has been considered just another herb to be routinely used by human beings. It was never singled out as an exception to standard herbal lore, but fit quite naturally in the traditional medical and nutritional systems.

While great reservations are found in traditional medicine about the use of plants, such as magic mushrooms, mandrake, jimpson weed, foxglove, rawolfia and other pyschoactive and cardiovascular plants, no record exists anywhere to suggest that similar concerns were ever directed toward ephedra.

So in recent years, ephedra has become a favorite herb of millions of Americans as a tool for safe and effective weight management. We have identified the active constituents, synthesized them, and these products, or the ephedra-related products, have been widely used throughout modern countries, civilized countries, if you will, not just Third World countries, but actually throughout Europe.

In fact, ephedrine-based weight loss products are the most popular weight management product in Europe and is rapidly becoming so in America.

Given the fact that obesity itself is more prevalent than ever before and that more people are dying of obesity-related disorders than ever before, the notorious syndrome X, the use of ephedra as a dietary supplement may be just the thing that we have been looking for.

Given its centuries-long reputation as a perfectly safe and useful herb, we have to ask the question, why all of a sudden is there this concern over ephedra's safety?

I can see two reasons for that. One is just flat out abuse. The second, I think, is an AER system that has failed us by creating misinformation rather than giving us the truth. The two reasons are intertwined.

The AER thing has been addressed. I just would like to say something about the area of abuse. While I sympathize with people who have lost members of their family to taking substances containing ma huang, whether that was the active constituent or not, I think that we are in a situation where we need better labeling for these things.

I don't think we are in a position where we should get rid of the—throw the baby out with the bath water, as it were.

We need to use the tool the way that it can be used safely, to help the millions who need it, at the same time devising labeling requirements and other regulations that reduce the risk of abuse. I thank you very much for allowing me to speak today.

Mr. BURTON. Thank you very much, Dr. Mowrey.

[The prepared statement of Dr. Mowrey follows:]

Ma Huang

Ancient and Modern

Historical Perspectives

Daniel B. Mowrey, Ph.D.

American Phytotherapy Research Laboratory

Mr. Chairman, members of the committee, thank you for inviting me here today. I was asked to testify about the historical use of ephedra or ma huang, the level of science in understanding usage, dosage, length of usage, known side effects, potential dangerous effects and potential benefits. I was further asked to clarify specific trends of ephedra use and how that has changed over time.

I. Roots

Some time ago I read where ephedra plants were found in a grave alongside the remains of a Neanderthal man, dating back about 20,000 years. I must admit to some hesitancy in citing this case -- it might just wind up in some Adverse Event Report. Yet the report does underscore just how long humans have using ma huang; it appears they even want to take it with them. In a related manner, in India and China, ma huang was considered to plant to promote longevity. Chinese references to ma huang go back to about 3000 B.C. References in India date back to at least 1500

B.C. The Romans used it, as did the Pakistanis, Iranians, and others.

Early American settlers in Utah brewed up a related species of ephedra; it became known as Mormon tea, or Brigham tea and was a favorite beverage among the exhausted and starving pioneers. Brigham Young was said to have enjoyed an occasional cup of his namesake tea on hot desert afternoons. Whether his wives shared this genteel -- or is it gentile? -- pleasantry is not known.

However, by far the greatest tradition of ma huang use comes from China and India where it formed an important part of traditional medicinal lore.

II. Traditional Chinese Medicine.

It is often remarked that ma huang (*Ephedra sinesis*) has been used in Traditional Chinese Medicine (TCM) for over 5,000 years. In an ancient sacred collection of religious Hindu writing (the Rigveda), a ma huang juice, called soma, was used to promote longevity. Over the centuries, its application has been refined to just a small extent. Historical as well as current thought on the applications of ephedra are listed in Appendix A. The gist of the matter is that in all countries in which ephedra is found, it is used treat respiratory ailments and to a lesser extent symptoms of cardiovascular distress. In ordinary language, ma huang was and is used in TCM to treat colds, flus, fevers, chills, headaches, swelling, asthma, hay fever, nasal congestion, aching joints and bones, coughs and wheezing, and to

promote perspiration (Leung and Foster)[1].

Ma huang is commonly used in a dose of 1.5 to 9 grams, most generally in the range of 5 to 6 grams; for asthma and increasing diaphoresis, the dose is 9 to 12 grams. This can be repeated up three times per day.

There has been little change in TCM applications of ma huang over the centuries. It is used today in TCM very much like it was a thousand years ago.

III. Modern Era: Traditional Applications

Ephedrine alkaloids were discovered in ma huang in the late 1800's by Japanese researchers. In the late 1920's Chinese scientists demonstrated the indirect sympathomimetic action of ephedrine. These scientists isolated and further clarified the structure of ephedrine. By 1930, an ephedrine monograph was able to list over 600 publications on the constituents and pharmacology of ma huang (Chen and Schmidt 1930)[2]. That report extensively reviewed research on the safety of ma huang alkaloids for human application.

Even though the synthetic drug ephedrine had been available in the U.S. since 1926, most physicians avoided prescribing it until the publication of the extensive safety and toxicity data on this alkaloid by Chen and Schmidt. By the mid 1930's, ephedrine was being widely used in the treatment of nasal congestion by U.S. doctors and pharmacists. Further developments over the next few decades led to the

widespread use of ephedrine in the treatment of asthma in recommended dosages up to 150mg per day. Thus, by the middle of the 20th century Western medicine had, through the invention of ephedrine, caught up with TCM uses for ma huang, and had done it on the basis of what had become a standard procedure in the West: namely, through the creation of a synthetic drug to mimic the activity of an herbal materials previously shown to exert the target activity (other examples include digitalis and reserpine). And so, ephedrine found its way into Western medicine the way many other drugs have: beginning in traditional medicine, moving on to the laboratory where the active constituent is analyzed and synthesized, and then to the public domain where the high degree of purification and standardization eliminates the need for the middleman, the guy who understands plant materials and how they should be applied.

Ephedrine had arrived. Next came the synthesis of yet another alkaloid naturally found in ma huang: pseudoephedrine. We recognize it easily as Pseudofed, a common drug used to treat hay fever and cold symptoms. Since then, millions of Americans have benefitted from the westernization of ma huang.

IV. Modern Era: New Applications for Ephedrine

The applications of ma huang being examined today have very little to do with traditional uses of ma huang. Thermogenesis. Weight loss. These or equivalent

terms are not to be found in TCM. And in fact the thermogenic application of ma huang actually stemmed from Western science, not from TCM or any other traditional medical system. Rather, the thermogenic properties of ma huang were discovered through the study of the properties of ephedrine hydrochloride. It was only by fortune that the whole plant exhibited the same property.

The idea for using thermogenesis as a method for weight loss grew slowly out of the scientific literature. It occurred as the result of a confluence of at least three independent lines of research. The first was searching for answers to the question: why don't hibernating animals freeze? The second avenue was pondering the question of cold adaptation in humans: why don't infants shiver? The implications of research in these two areas for weight loss were gradually manifested as scientists began asking questions about discrepancies in assumptions underlying obesity: why does eating less not necessarily lead to weight loss, and conversely, why does eating more not necessarily lead to weight gain? The answers to these questions produced nothing less than a paradigm shift in our thinking about the cause, treatment and cure of obesity. Appendix B gives a more detailed overview of this historical process.

Briefly, the commonality among these areas of inquiry proved to be a little known structure in the body called brown adipose tissue, or BAT. BAT is where a great deal of body heat is produced; it is the organ of thermogensis. In fact, it does

nothing else but create heat. Babies have a lot of it and do not need to shiver. Adults have less per unit body mass and so must shiver to stay warm. Hibernating animals have a lot it and so they don't freeze during the winter months. And thin people have enough to burn off all excess dietary calories, so they don't get fat. Obese people have dysfunctional BAT, so they store excess dietary calories as body fat.

The key to obesity is reactivating BAT. *Ephedrine is the only known effective substance for doing that.* Furthermore, ephedrine also helps improve basal metabolism in ways that reduce body fat. While the search for more effective and -- more importantly -- novel drugs goes on at a rapid pace, ephedrine remains the substance of choice for stimulating thermogenesis.

Now, to be sure, this is a whole new area of application for ephedrine. Considerable research has been directed toward it. That body of research clearly supports the safety and efficacy of ephedrine. The vast majority of the research was done on a mixture of ephedrine and caffeine in a ratio of 20mg ephedrine/200mg caffeine taken three times per day, for a total daily ephedrine dose of 60mg. Contrary to popular opinion and FDA assertions, the caffeine is not added for its stimulant properties, but for its ability to disinhibit BAT thermogenesis thereby assuring the relatively small 60mg dose of ephedrine will be effective. That research is also reviewed in Appendix B.

V. Modern Era: New Applications for Ma Huang

It was only a matter of time before members of the dietary supplement industry began to suspect that ma huang, due to its content of ephedrine, might regulate body weight in a manner similar to that of ephedrine hydrochloride. It also did not take a rocket scientist to determine that caffeine present in several different plant species might also contribute to the overall effect. It was simply a matter of standardizing the plants to deliver a consistent amount of the ephedrine or caffeine and then administering the appropriate dose.

There was the question of whether the ephedrine alkaloids in ma huang behaved like the synthetic. They do.[3]

There was the question of whether regulatory agencies could quickly, cheaply and effectively measure the amount of alkaloid in the products of commerce and also determine whether they were spiked with ephedrine hydrochloride. Adequate procedures were developed,[4, 5] some by the FDA itself.

There were questions about adequate labelling. After much debate, the labeling issue has been satisfactorily resolved. With FDA's help, we should see an end to wild-eyed claims.

All of this research activity is well within the province of herbal medicine. Since herbs are regulated as foods, I prefer to refer to herbs as medicinal foods, and

would champion a regulatory drive to establish such a regulatory category. Medicinal foods should bear carefully structured labels with adequately supported claims. Proactive efforts should be made to educate people about who should and should not use ephedra products to regulate weight and about hazards of abuse.

Along these lines, the two abuse-happy segments of the industry need to be dealt with harshly and immediately: Owners of multi-level companies should be held accountable for false labeling by their members; and body builders should be educated about the dangers of misusing all forms of dietary supplements (I suppose this is like getting people to stop abusing aspirin, cold medicines, aerosol paint and glue). Success in those two areas would eliminated over 95% of all serious adverse events.

At the outset I indicated that apparently even a Neanderthal was bright enough to recognize the value of ma huang. I imagine that along about that time, early man also became acquainted with tools, like shovels and axes useful in building and gardening and clearing the land. But do we want to outlaw the axe simply because Lizzy Borden used it to chop up her family? Ma huang has become a useful tool for millions of Americans trying to get rid of excess body fat. Do we want to restrict the freedoms of millions just to protect the health of a few foolish zealots?

I was there in the early 90's when the ma huang revival occurred. For about

seven years I have been investigating the thermogenic properties of ma huang. During that time I have witnessed both appropriate and inappropriate applications. There were products with reasonable and standardized versions of ma huang and ma huang plus caffeine. There were some unstandardized versions also. Public consumption patterns ran from the circumspect to the outlandish, but never approached the level of abuse surrounding the use of the 25mg ephedrine hydrochloride pill. There were and still are the euphoric compounds, but the amount of ephedrine in these is fairly low. Normally, the danger in these compounds comes not from the ma huang but from hallucinogenic nutmeg extracts high in myristic acid, from the PPA, and from other questionable substances commonly added to such products.

Unacknowledged by FDA is the fact that over the years things have improved and will continue to improve. I am outraged at FDA's recent tactics of releasing to the press statements to the effect that AERs are fewer but adverse events are more serious, of trickling out to the press individual cases of supposed deaths and other serious events, and yet failing to open these AERs for public review with the lame excuse that they haven't had time. They are playing the press for fools and the American public will suffer for it. Already, there are thousands of obese Americans who will not use ma huang because of the negative press. We all implicitly know that

FDA has the safety and health of Americans at heart. Thus, when the occasional missfire occurs, we are ill-prepared to critically deal with it.

VI. FDA's Proposed Rule: A Neat Trick

In my opinion modern research has clearly established both the efficacy and safety of ephedrine. The millions of doses of ma huang consumed every year by Americans without serious adverse events argues powerfully for the safety of ma huang when consumed according to label directions. The most current action in the history of ma huang is an attempt by the FDA of the United States to curtail the natural evolution of ma huang as a valuable plant in service to the health needs of Americans and to restrict freedom of choice in this critical area. In my opinion, testimony before this committee today will unequivocal demonstrate the mendacity of that action.

An objection may be raised on the basis of the accumulated AERs presented as evidence of the danger of ma huang use. In fact, FDA's entire case rests substantially on those reports. While it is not the primary purpose of this paper to critique AER's (that is being handled by other members of this panel), I do want to mention that I reviewed every single AER available in the docket and found no proof that ma huang *when consumed as directed* on the label, provoked any serious adverse event. Furthermore, the supposedly huge amount of clinical data on ephedrine toxicity when

consumed at levels of 150mg per day failed to materialize. Instead, FDA cited two or three case histories in which hundreds and thousands of milligrams were ingested over several months or years. Also lacking from the FDA data are denominator data. So I provided my own. For example, I discovered that hundreds of people die every year in doctor's offices on treadmills. Is it a surprise, then, that out of the millions of Americans using ma huang, one of them happens to experience exercise-related injuries? Appended to this document is my review and findings. Frankly, I was surprised. Like most members of the medical and alternative medicine communities, I had assumed that all of the negative press being generated by FDA was the result of a careful analysis of case histories. Sadly, nothing could be further from the truth. The very selective group of AER's listed in the proposed rule, the very AERs that should best represent and support the propositions of the proposed rule in fact did more to support the safety of ma huang than they did to substantiate a threat of toxicity. There are many levels, economic, political, scientific, medical, to name a few, on which one can and should be appalled by FDA action on this issue.

Furthermore in the proposed rule, FDA would confuse the issue. By not clearly defining adverse event or the nature of "serious" in the proposed rule, it can then go on to list as "serious" events which are clearly not serious, and by extension, use the term "adverse" to imply all kinds of bad things. In fact, any unwanted event is

adverse; thus there can mild, moderate and serious "adverse" events. But **elsewhere,** FDA has defined adverse in relation to ma huang to be death, stroke, seizure, heart attack. Tremor, palpitation, headache, nausea and anxiety are mild adverse events. They are also transient, disappearing within a few days as tachyphlaxis sets in.

FDA, by limiting the duration of ma huang consumption to a week guarantees that tachyphlaxis will not occur and thereby negates one of the great advantages of ma huang. It also guarantees increased complaints of mild adverse events.

FDA, by arbitrarily limiting the daily dose to 24 milligrams, ignores all research that show that a daily dose of 60 milligrams is required. A company seeking the sell ma huang for weight loss *must* conform its product to available research, all of which shows that if ephedrine and caffeine are involved, the recommended dose *must* be 20mg ephedrine and 200mg of caffeine three time per day. There is absolutely no research to support a dose less than that. In fact, any attempt to market an ephedrine/caffeine product with a smaller dosage schedule would be subject to FTC filings and summarily removed from the market.

Hence, FDA's proposed rule is thus a cleverly crafted trick. In the government's search for a scientific basis for ephedrine/ma huang utilization and standardization, FDA's rule is worse than useless; it has motivated Americans everywhere to accuse FDA of some pretty serious things. Over the course of the past

couple of years, I have heard people state outright that they believe the proposed rule stands as an affront to science, a slap in the face to American enterprise, an impediment to a common sense resolution, a destructive influence on statistical methodology in the medical arts, a waste of taxpayers' money, and a sloppy attempt to dismantle DHSEA.

Frankly, I am embarrassed by such remarks, and by my inability to refute them. Coming from a more orthodox scientific background, I have witnessed many victories by FDA over notorious quackery. But in this case, I can't help but believe FDA crossed over some lines and entered forbidden territory. Hopefully, this will be just a small blip on an otherwise illustrious heritage.

VII. Summary

Over the ages, the use of ma huang has always been to lessen the impact of serious disease, whether it was respiratory, cardiovascular, or obesity-related. The shift in modern times to obesity treatment has resulted in billions of doses having been consumed over the last seven to eight years.

The consumption of ma huang for obesity has been the direct result of a paradigm shift in our thinking about the causes, treatment and cure of obesity itself. BAT thermogenesis is a young science; the genetic basis is just being addressed.

In this volatile climate of a new science for an important ailment, combined

with brand new applications for ancient herbs, there is bound to be a period of adjustment. However, by and large, we are emerging from that confusion, with fairly clear ideas of what is and what is not appropriate. On the one one hand, FDA's proposed restrictive action appears to be too little, too late. On the other hand, its concerns about labeling seem to be right on target; good labeling, endorse and enforced by FDA, would easily solve 99% of any remaining problems.

It seems to me that the force of public opinion here will not be denied. Until other agents are found that promote thermogenesis in brown adipose tissue, ephedrine and ma huang remain our only effective *long-term* treatments for obesity. I can't help but think that any move to restrict Americans' access to this herb must be considered a grave error.

Thank you for this opportunity to address this committee on this important issues.

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1. Leung, A.Y. and Foster, S., Common Natural Ingredients used in Foods, Drugs andCosmetics, NY, John Wiley, 1995.

2. Chen, K.K. and Schmidt, C.F., *Medicine (Baltimore)*, 9, 1-117, 1930.

3. Gurley, B.J., *et al.*, "Ephedrine pharmacokinetics after the ingestion of nutritional supplements containing Ephedra sinica (ma huang)." *Ther. Drug Monit.*, 20(4), 439-445, 1998.

4. Cui, J., *et al.*, "Analysis of alkaloids in Chinese Ephedra species by gas chromatographic methods." *Phytochemical Analysis*, 2, 116-119, 1991.

5. Betz, J.M., *et al.*, "Chiral gas chromatographic determination of ephedrine-type alkaloids in dietary supplements containg ma huang." *JAOAC Int.*, 80(2), 303-315, 1997.

Appendix A

Traditional Applications of Ephedra in Traditional Chinese Medicine

One of the most cogent modern text on TCM is *Oriental Materia Medica* (1986) by Hong-Yen Hsu, Ph.D., and associates[1]. It reviews the history of TCM and presents a concise description of the TCM uses for each plant. Under the heading for ma huang, the traditional uses are listed on page 52:

> Actions: Induces diaphoresis, resolves surface, ventilates the lungs to relieve asthma, regulates water metabolsim
> Applications: Febrile disease due to exterior-excess, fever, chillphobia, anhidrosis, ostealgia, arthralgia, cough with dyspnea, edema, edema due to wind

Hsu also lists the pharmacological properties of ma huang *as established by Chinese scientists* working within the TCM system. These properties are as follows:

> (1) Relieves spasms of the bronchi: ephedrine and pseudo-ephedrine relaxes the smooth muscles of the bronchi, the bronchodilating effect being slow but long-lasting. Ephedrine stimulates both the central

and sympathetic nervous systems.

(2) Sudorific and antipyretic effects: The aqueous extract when given orally to mice will induce sweating on the soles of the paws, the amount of swelling increasing with oral dose.

(3) Hypertensive activity: Ephedrine constricts blood vessels, thus increasing blood pressure.

(4) Diuretic effect: Pseudo-ephedrine exerts a marked diuretic effect by dilating renal blood vessels.

(5) Antiviral effect: The essential oil inhibits influenza virus.

(6) Dilates the pupils: Applying a 10% solution to the eyes has the effect of dilating the pupils for several hours.

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1. Hsu, Hong-yen, *et al.*, Oriental Materia Medica: A Concise Guide, Keats Pub., New Canaan, CT, 1986.

Appendix B

A Short History on the Emerging Science of Brown Adipose Tissue Thermogenesis

The study of hibernation led to the discovery that hibernating animals have a special organ called brown adipose tissue, or BAT, whose sole function is to create heat.[1] Exposure to the cold is what stimulates BAT to begin producing heat. Further studies on BAT revealed that it contains a special protein called the uncoupling protein (UCP) that uncouples oxidative phosphorylation thereby diverting to heat production calories that would normally be converted to metabolic energy.[2] UCP is found *only* in adipose tissue, most prevalently in brown adipose tissue. Defects in UCP would result in faulty thermogenesis and lead to increases in body fat stores.[3]

Soon researchers found that human infants have a great deal of BAT relative to their body mass. Hence, exposure to cold in infants stimulates sufficient heat production in BAT to compensate for the cold. Shivering as a means of heat production first appears when the human body mass has increased to a point at which BAT thermogenesis is no longer sufficient. Adult humans exhibit the phenomenon of cold adaption. That is, when exposed to a cold climate for an extended period of time, they gradually experience an increased tolerance. The underlying adaptive mechanism is brown adipose tissue thermogenesis (BATT).[4, 5]

While research along these two lines was unraveling the mystery of hibernation and cold adaptation, scientists engaged in the study of obesity were struggling with paradoxes of the energy equation. The fundamental axiom of weight management is the simple equation that energy in (as from food) must equal energy out (as in work). When the energy in side is higher than the energy out side, then excess energy is stored as body fat. Conversely, when the energy out side is higher than the energy in side, some loss of body weight must occur. The fact of the energy equation underlies all weight loss programs that seek to reduce body weight by raising the energy out side by exercise, or by lowering the energy in side by dieting, or both. The problem is that neither program works very well, as millions of dieters will confirm. The body simply has too many adaptive mechanisms for defeating these measures that do not address the underlying problem. This is not to say that exercise is not valuable. It certainly is, and Americans could all stand to do more of it, but as a method of long-term weight loss, it simple doesn't work for most people.

And then there was that ugly bit of research performed by Derek Miller in 1967 that showed that college students fed thousands of excess calories on a daily basis for extended periods of time did not necessarily gain weight.[6, 7] Some did, but others did not, and there were some subjects, in fact, that actually lost weight. What was happening to those extra hundreds, even thousands, of calories? If they weren't being

stored, and the BMR measurements showed that they weren't being used, then where were they going? Miller suggested that those individuals who gained weight did so not because they ate too much, but because they had a defective thermogenic mechanism, probably because they were experiencing deficient sympathetic stimulation medicated by norepinephrine. He then suggested (the first person to seriously do so) that ephedrine could be used to treat obesity. These early ideas of Miller flew directly in the face of conventional wisdom about the causes of obesity, which held firmly to the idea that 'gluttony' was the ultimate cause. It would take several years for the medical community to begin to seriously entertain Miller's notions. And so, over the course of the next several years, researchers took stabs at explaining Miller's results using popular theories. Wasting cycles were proposed, but none could be found that satisfied the requirements. The liver was the organ most often proposed as the site of this activity, but it couldn't be proven. Brown adipose tissue was suggested, but dismissed early on since it appeared that the adult human did not possess enough to make a difference. In fact, the idea that adults do not have enough BAT to make a difference is still held by most medical professionals. Meanwhile, however, a whole science of BATT has sprung up almost overnight. What happened was that someone finally decided to measure the degree of thermogenesis adult humans were capable of. The answer was astounding. Apparently, thin humans have substantial thermogenic potential.[8] Obese humans, on

the other hand, have small, poorly functioning BAT stores. While most dietary calories are consumed in meeting the demands of metabolic processes, a small percentage remains that the body must deal with. It can either burn these calories off in BAT, or store them as body fat. Over the years, this begins to make real difference in body composition. It has been estimated that even a 1% deficit in thermogenesis over a person's adult lifespan can lead to body fat values of up to 40%.[9] I suspect that in many people, BAT has ceased to operate at all. It needs to be turned back on.

Could obesity really be a simple function of poor BAT thermogenesis? Well, the science is young. But the theory nicely fits most of the results of obesity research, from leptin to polymorphisms of the Beta-3 adrenoceptor, from fat mice to fat people. Fat or thin could simply be a function of BATT. It is my opinion that the final common pathway for all forms of obesity, whether the result of some genetic anomaly or the result of something as common as hypothyroidism, will be shown to be dysfunction of brown adipose tissue thermogenesis.

Ephedrine entered the picture once it was found that BAT and hence BATT are under the control of the sympathetic nervous system.[10] Ephedrine was also of interest because it could stimulate rises in energy expenditure in other tissues under sympathetic control. The major peripheral neurotransmitters and mediators for the effects of exercise are norepinephrine (NE) and epinephrine. Hence, thermogenic adrenergic agonists should be ideal candidates for the treatment of obesity. Although

several potential adrenergic anti-obesity drugs are being studied, *ephedrine is currently the only available drug of this type.*[11]

Early experiments with ephedrine in animals proved hugely successful.[12] The BAT hypothesis gained the status of theoretical model. Based on the known physiology of the synaptic junction separating sympathetic nerve endings from BAT, it was reasoned that sympathomimetic activity of ephedrine in BAT could be made more effective at lower doses if certain molecules in the synapse and in the membranes were inhibited. The way it works is like this: Ephedrine stimulates the sympathetic nerves peripherally (not centrally) to release norepinephrine from the nerve endings in the vicinity of BAT. NE traverses the synapse and attaches to receptors on the surface of BAT cell membranes. The signal is then carried across the membrane and into the cell where the events known as the thermogenic cascade commence. But along the way there are molecules that provide negative feedback on the whole process -- that is they tend to inhibit the chain of events that produce thermogenesis.

Caffeine was introduced into the ephedrine-initiated chain in order to inhibit some of the inhibitors.[13] This process, called disinhibition, or releasing certain events from the effect of inhibitory substances, is the complete opposite of the traditional uses of caffeine as a stimulant. *Without understanding this, it is impossible to comprehend the historical importance of combining caffeine with ephedrine.*

Admittedly, even many manufacturers of ma huang/caffeine combinations do not understand the truth of the matter, and are prey to the same mistake promulgated by ma huang antagonists to the effect that caffeine is added because of its *stimulant* properties. Although some stimulant action may occur at the dosage levels required for disinhibition of BAT, that is not the principle reason for the combination.

Likewise, aspirin was discovered to further disinhibit the activity of ephedrine.[14] It is the opinion of some professionals that ephedrine in the recommended dosage range could not be effective. There would be some truth to that statement were it not for the presence of disinhibitors. At any rate, moderate thermogenesis in BAT (and possibly elsewhere in the body) is achieved with a typical ma huang/caffeine combination containing 20mg ephedrine and 200mg of caffeine administered three times per day. This 60mg dose is less than half the 150mg dose required for the control of asthma.

The combination of ephedrine and caffeine in doses described above has been hugely successful in Europe where it currently accounts for about 80% of the market for weight control agents.[15] The reason for this popularity is simple: effectiveness without serious side effects. The problem of serious side effects was an early issue with ephedrine as a proposed weight control agent. It was reasoned correctly that humans would need to use it for several months to gain the desired degree of weight loss. Thus, it was necessary to devise a means whereby unwanted side effects could

be minimized without eliminating the beneficial properties. The solution was already at hand. It was already known that repeated dosing leads to a reduction in cardiovascular and pulmonary results. Tolerance or tachyphylaxis develops. Hence, if any adverse events are to occur they will appear within the first few days, and tend to dissipate after that. But does the same happen in BAT? And is it possible to administer a dose low enough to stimulate BAT but not so large as to produce serious adverse events?

The questions were answered through further scientific inquiry. First, it was found that BAT actually increases in mass with repeated stimulation by ephedrine and by caffeine.[16, 17] Second, while tachyphylaxis does occur for the cardiovascular and pulmonary events, BAT appears to increase in sensitivity.[18] In other words, a down-regulation of unwanted events occurs, while an up-regulation of BAT responsiveness occurs. Third, with the help of disinhibitors, it is possible to administer a dose sufficient for BAT stimulation, without concurrent heavy stimulation of receptors in other areas of the body. This latter effect appears to be the combined result of the presence of the uncoupling protein and a special receptor class found almost entirely in BAT: the beta-three adenoceptor.[19] While the importance of the beta-three is not without controversy at this time, several investigators believe that stimulation of this receptor may be the key to BAT thermogenesis. In fact, much research today is dedicated to the search for a substance that selectively stimulates

this receptor. Norepinephrine is a non-selective agonist, stimulating all three types of beta receptors, but the thought is that at low doses, in combination with disinhibitors, ephedrine can release just enough NE to stimulate alpha-three with just a moderate stimulation of beta-one and beta-two.

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Mr. BURTON. Dr. Dickinson, it is nice seeing you again.

Dr. DICKINSON. Thank you very much, Mr. Chairman.

The Council for Responsible Nutrition is a trade association of dietary supplement manufacturers representing some hundred member companies who are deeply committed to producing safe and quality products.

We are proud of the safety record of dietary supplement products overall, but we recognize that there is a need for an adverse reaction reporting system because any product, including preapproved products, can result in unexpected effects when taken by millions of people in the general population.

Therefore, the adverse reaction reporting system is a very important signal to us where there may be some errors in product manufacture or some other issues that are causing consumers to be harmed, and it is a valuable indication of that need for action.

We share the concerns expressed by the chairman in your opening remarks regarding the need for FDA resources to handle these systems appropriately, the need for prompt reporting of adverse reactions on the public system.

We question the appropriateness of listing the company name and the product name as part of the table of contents. Mr. Levitt was referring to the publicly available website. The AER system is a table of contents of the system, and I would like to suggest an alternative to the kind of listing that we see on the current system.

We also share the chairman's concern about the need to correct errors that may creep into initial listings; and, actually, our new proposal may address some of that concern.

There is an overwhelming need to evaluate the strength of the association, both in terms of the seriousness of the reactions and the nature of the causality of the product taken and the effects seen.

I would like to spend just a couple of minutes describing what may be a very useful new way of approaching the development of this system.

In our statement that we submitted prior to this hearing, we suggested that there might be a three-step system that could be adopted for making these reports publicly available.

First of all, as soon as FDA receives the report, we believe it should immediately become available on the public system, that is, on the website. We would suggest, however, that that initial posting perhaps should only include a description of the generic nature of the product involved and a description of the ingredients of that product, if that is available, and the nature of the symptoms that are observed in the adverse reaction.

We see no reason, no compelling reason, why the name of the company and the name of the product should be part of this very first initial product listing which is only an indication that a report has been received and has not been at this point evaluated in any way.

Therefore, we would suggest that FDA consider having a separate part of its reporting system that is reserved for the initial reports where there would only be generic information about the reaction.

We agree with Mr. Levitt that the priority is that as soon as FDA receives these reports, they should immediately purge them of personal information that is not releasable, so they may be released in a very prompt fashion.

We also believe that the FDA should immediately share those reports with the manufacturer or, in the case where the manufacturer has not been identified, with trade associations representing the industry so they may work with FDA to provide more complete information about the nature of the product, about the nature of its expected effects, and also assist in investigating the particular adverse reaction report.

Therefore, we would suggest that as soon as FDA has conducted the second phase of the investigation, that is, has shared the report with the manufacturer and has done some analysis of the likely causality involved in the report, that it be moved from this initial report section, which is a summary form into one of two more permanent report sections.

One of those two sections would be reserved for adverse reactions that the FDA has, in fact, determined are likely to be related to the product itself. And in that case it may be appropriate to include in that listing the name of the product and the name of the company after the company has been notified of that.

We think that there should be a third section of these reports which will be reserved for reports which are determined definitely not to be related to the product taken or about which there is insufficient information available to make a determination.

Therefore, we would end up with a three-part reporting system, an initial part which is a summary, a second part which is essentially the ones that are either not related to the product or about which there is not sufficient information, and then a third part which would really be the core of the permanent record and would be the basis for FDA's future analysis of any action to be taken which would be limited to those reports that have been evaluated and where there is sufficient evidence to believe that the report, the adverse event is, in fact, related to the product.

We think that this would improve the ability of FDA and the industry and other health professionals to use these adverse event reports in a productive way to address questions that need addressing as promptly as possible.

Thank you very much.

Mr. BURTON. Thank you, Dr. Dickinson.

[The prepared statement of Dr. Dickinson follows:]

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IMPROVING THE ADVERSE EVENT REPORTING SYSTEM FOR DIETARY SUPPLEMENTS

Testimony of Annette Dickinson, Ph.D.
Vice President, Scientific and Regulatory Affairs,
Council for Responsible Nutrition
before the
Committee on Government Reform
May 27, 1999

The Council for Responsible Nutrition (CRN) is a trade association representing the dietary supplement industry. We appreciate the opportunity to participate in this discussion of ways to improve the quality of adverse event reporting for dietary supplement products. CRN and its 100 member companies are committed to providing safe, high quality dietary supplements to consumers who are seeking to improve or optimize their health. We believe that marketers of dietary supplements have the responsibility to assure the safety of their products, and we are proud of the safety record of dietary supplements as a product class. At the same time, we recognize the need for a postmarket surveillance system to serve as an early-warning signal when unanticipated problems occur for any reason.

CRN has been working with FDA in attempting to evaluate and respond to adverse reaction reports on dietary supplements since the agency's new reporting system for special nutritional products was developed in 1993, soon after establishment of the FDA Office of Special Nutritionals. The reporting system covers medical foods and infant formula, as well as dietary supplements, but our focus today will be solely on dietary supplements.

CRN believes FDA's current adverse event reporting system for dietary supplements needs some improvement, and we have several recommendations that might be considered by the agency and the Congress. In this statement, we will outline some of the problems that we have identified and some potential solutions deserving of further discussion.

We recognize that some of our suggestions would require more resources than FDA currently has available, and we fully support the need to make additional resources available to fulfill these needs. In fact, it is our understanding that the agency is already scheduled to receive some additional resources to improve the handling of adverse reaction reporting systems for special nutritionals.

Need for Prompt Reporting

An adverse event reporting system must alert not only FDA but also the industry and health professionals to the existence of potential problems. To meet this requirement, reports must be made available promptly. At the present time, reports relating to dietary supplements appear on the Web. However, reports are updated only a couple of times a year. Thus, there may be a substantial delay between the time FDA learns of an adverse reaction and the time anyone else learns about it.

For example, FDA took enforcement action in January of this year against products containing GBL, and CRN supported that action. At the time, the agency said it had 55 reports of serious adverse reactions, including one death. When an additional warning was issued in early May regarding a related product, FDA said it had a total of 122 adverse effect reports, including three deaths, on the three related products (GBL, GHB, and BD). Even now, most of these cases have yet to appear on the adverse reaction reporting system on the Web.

Ideally, adverse reaction reports should appear on the Web as soon as FDA learns about them. In this manner, industry as well as consumers and health professionals could be alerted as soon as possible to a developing problem that may require action. We would recommend that the initial report appear in a generic format, perhaps including only the general product description, the ingredients, and the nature of the event.

Appropriateness of Listing Company Name and Product Name

CRN believes further thought needs to be given to when and whether a report needs to include specific identification of the company and product involved, beyond a generic description of the product type. This will be further discussed below, in the context of a proposed new system structure.

Need to Correct Errors in Reporting

Sometimes an initial case report may incorrectly identify a company, its product, or the ingredients of the product. This may happen because the consumer or a health professional did not have the correct information available at the time the report was submitted. Under the current system, there appears to be no mechanism for correcting inaccurate information in the initial case report. There needs to be a way of amending

incorrect information. Far from undermining the integrity of the original report, this would assure that the reports are as complete and accurate as possible. A footnote or some other mechanism could be utilized to explain the reason for any changes.

Need to Indicate Seriousness of Reported Events

FDA's adverse reaction reporting system has no provision for designating a case as mild, moderate, or severe. However, such classifications are used in other reporting systems, including the Poison Control Centers' reports. We would recommend adding a designation of severity to each case report.

Need to Evaluate Possible Causality

There is currently no evaluation of the likelihood that adverse reports dealing with dietary supplements are causally related to the product used by the consumer. This could lead either to falsely concluding that all of the reports are causally related to given products, or that few if any of the reports are causally related to given products. Either conclusion would undoubtedly be incorrect.

There is ample precedent for evaluating likely causality, even when dealing with passive reports and incomplete information. If some reports are so sparse that no analysis can be done, then that also is useful to know.

FDA currently has no formal system for adverse reaction reports related to foods, but the agency has on occasion initiated a special data collection effort for some food additives about which there were safety concerns. In FDA staff reports on the adverse reactions to aspartame, it is clear that adverse events were classified as to severity, with severe reactions being designated as Type I. In addition, reactions were classified into four groups according to the strength of the association with aspartame. It is noted that about 30% of the cases lacked sufficient information to classify them according to strength of association. This illustrates that classifying adverse event reports is feasible and has in fact been done for some food ingredients.

FDA staff members have recently made presentations using the veterinary medicine adverse reaction reporting system as an example of applying causality analysis. Factors taken into account in evaluating causality include:

1. Whether effects are consistent with the known pharmacology of the product.
2. Whether there are other explanations for the effects observed.
3. Whether there is a reasonable temporal relationship between using the product and observing the effect.
4. Whether there is evidence of an overdose.
5. Whether the effects went away when use of the product was stopped.
6. Whether the effects reappeared on rechallenge.

Applying these criteria to approximately 3000 adverse reaction reports received in a recent year, relating to veterinary medicines, evaluation revealed that:

- Only 1% of the reports could definitely be associated with the product.
- 31% of the reports were probably associated with a given product.
- 45% of the reports were possibly associated with a given product.
- 12% were definitely not related to the product.
- 11% were lacking adequate information to evaluate possible causality.

CRN believes that it is important to apply causality analysis to the dietary supplement adverse event reports, to allow better evaluation of the likely association between a given case or set of cases and a specific product or class of products.

Reconsideration of the Structure of the Reporting System

Under the current system, a company's name and its product name may appear on the adverse reaction reporting system, associated with a case report, without the company even being aware of the existence of the report. Further, a company that becomes aware of a report may not even be able to obtain the background information on a case, because the agency has not had a chance to purge the record of personal information regarding the identity of the consumer or patient.

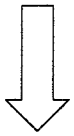
We would like to take this opportunity to suggest that all affected parties give consideration to the possibility of developing a new structure for the reporting system. A new structure should facilitate immediate reporting of generic information on adverse reactions, provide incentives for manufacturers and FDA to act quickly to determine the facts of a case, ensure that companies are promptly provided with background information, and prevent the false attribution of an event to a particular company or product. We would strongly recommend that FDA seek comments and suggestions from all interested parties, as it moves forward with changes to the existing structure or implementation of a new structure.

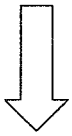
A new adverse reaction reporting system could potentially have three components:

- a section for initial, unevaluated reports;
- a section for reports which have been determined to be unrelated to a given product, or which lack sufficient information to make a determination; and
- a section for reports which are definitely, probably, or possibly related to a given product.

This structure is described graphically below.

UNEVALUATED REPORTS
(Generic information, at initial listing)





UNRELATED/INDETERMINATE CASES
(Generic information)

RELATED CASES
(Full information)

FDA initially might put generic information on each new case report into the "Unevaluated Reports" section. This initial information should include only a generic description of the type of product involved, a list of ingredients, and a description of the adverse reaction. FDA would immediately purge the case report of personal information and send it to the product manufacturer, allowing an appropriate timeframe to comment or provide additional information. Meanwhile, FDA would proceed with an evaluation of the seriousness of the adverse reaction and a causality analysis.

If the causality analysis shows that the product is not likely to be related to the adverse event, or if there is insufficient information available to make a determination, then the report might be moved from the "Unevaluated" section to the "Unrelated/Indeterminate" section, again with only generic information on the nature of the product mentioned.

If the causality analysis shows that the product is definitely, probably, or possibly related to an adverse reaction, then the report might be moved from the "Unevaluated" section to the "Related" section. Only at this point would the verified report receive a full listing, including the name of the product and the manufacturer.

This concept for a new structure is offered as an idea intended to spur further discussion among the industry, the agency, and the Congress.

Commitment to Cooperative Action

On behalf of its member companies, CRN is committed to working cooperatively with FDA and Congress to improve postmarket surveillance for dietary supplements. We believe it is critically important to have an accurate, fair system that can quickly flag emerging, unanticipated health problems, in order to permit the industry, the agency, and health professionals to respond promptly when corrective action is needed.

Mr. BURTON. Ms. Schlendorf, we appreciate you being here, both you and Ms. Michal; and we are very sorry about the experiences you have had.

Ms. SCHLENDORF. Thank you.

Mr. Chairman, members of the committee, my name is Karen Schlendorf. To me Peter Schlendorf is not an adverse event but my youngest child who, like too many others, suffered from the fatal effect of a herbal supplement which contained ephedrine.

I believe that I am speaking for so many people who can no longer speak for themselves, Kristopher Michal, Rosanna Porras, to mention a few; but let me tell you about Pete Schlendorf.

As a mother, it is very difficult to put into words the depth of my feelings for my youngest son. Pete was the joy of my life. From the day he was born, Pete was someone very special. He made me smile every day, and I thanked God that I had been blessed with such a wonderful gift.

My three children meant the world to me; and as a full-time mother, I enjoyed every minute that I spent with them. On the day that I began my job as a high school guidance counselor, Pete, who was then 10, picked a bouquet of flowers from our garden for me.

I had always given the children a small gift on the first day of school and told them how proud of them I was, and now he was doing the same thing for me. He was always a kind and thoughtful person who made people glad that they knew him. He brightened a room every time he entered it.

He was always the center of attention, not because he asked for it, but because it seemed to come to him naturally. Pete was bright and funny, athletic and talented and a leader among his peers. I was proud of his accomplishments and prouder still of the man he was becoming.

Then one day the unthinkable happened. He died. Pete had gone to Florida on spring break with some of his friends. On a cold and overcast day, they decided to explore some of the shops along the beach. All week they had seen ads and banners promoting herbal supplements of all kinds. They went into one of the shops and decided to try one.

It is all natural, safe, harmless. The store clerk said that she and her friends took 10, 12 of them all the time, made them feel great and gave them lots of energy. So the boys tried them.

Pete took somewhere between four and eight pills and almost immediately began to feel strange. His heart rate was faster, he felt tingly, hot all over and had a pounding headache. He took a shower, but it didn't help.

He told the other boys to go out, and he would lie down for a while; and when he felt better, he would join them later. The last time his friends saw him alive, he was sitting on the edge of a bed reading the label on the box. What had he taken? What was wrong? What should he do? There was no help on that box.

It took weeks, months for us to understand what happened to our beautiful, wonderful, healthy son. At least now we know the facts. But I don't know that we will ever really understand. Pete died because a company cared much more about profits than about lives. Pete died because he had an unfortunate chance encounter with Ultimate Xphoria.

The manufacturers of this product have admitted to us their irresponsibility and their callousness. They have admitted that they are not sure how many or which additional herbs were in each batch.

They claim not to know where the ma huang came from, which part of the plant was used, the time of year it was harvested, or how strong the concentration was. They didn't know, or perhaps they didn't care; but my son died because Ultimate Xphoria was improperly manufactured and irresponsibly marketed toward young people.

A number of ingredients in this product posed a risk to Pete or any other healthy individual. Combined, they caused an insurmountable risk of harm. I know that there is a great deal of information in publications and on the Internet that disputes these truths. I have read them myself. But this is the truth.

I have a copy of Pete's autopsy, something no mother should ever have to see; and it shows beyond a shadow of the doubt that the only thing in Pete's system was the ingredient in this product. He had been on spring break with his friends, but there was no evidence of any drug or alcohol or anything else except the lethal herbal supplement that he bought over the counter in a little shop on the beach.

Ephedrine is a drug. It has been known as a drug for over 5,000 years. No amount of legislation will make it a food. Proponents of ephedrine-containing supplements like to say that the Chinese have used it for centuries. They have, through practitioners who prescribe it as part of their traditional medicine, not for weight loss, not for energy boosts.

Scientists have agreed on what ephedrine does. It dilates bronchial muscles, contracts nasal mucosa, raises blood pressure, acts as a cardiac stimulator. Although there may be some disagreement as to a safe limit of ephedrine, I do not dispute that in proper hands, ephedra can be appropriate and safe.

However, the Dietary Supplement Health and Education Act of 1994 has allowed irresponsible persons to contaminate the marketplace with false claims and dangerous marketing. I doubt that it was the intention of this governmental body to allow people like those who caused my son's death to get rich at the expense of America's youth.

I fully understand that there are many people and certainly many manufacturers making millions of dollars from these products who don't want to hear any of this, but I would hope that my government would want to hear this.

Filing an adverse event report was our vehicle to the truth, and I did this in honor of my son, Peter Charles Schlendorf.

Mr. BURTON. Thank you very much. That was a very touching statement.

[The prepared statement of Ms. Schlendorf follows:]

To: Government Reform and Oversight Committee

From: Karen Schlendorf

Re: FDA Adverse Event Reporting System and Dangers of Ephedrine

Date:May 27, 1999

To me Peter Schlendorf is not an adverse event but my youngest child who like too many others suffered from the fatal effect of an herbal supplement which contained ephedrine. I believe that I am speaking for so many people who can no longer speak for themselves; Kristopher Michal, Rosanna Porras, to mention a few. But let me tell you about Pete Schlendorf.

As a mother it is very difficult to try to put into words the depth of my feelings for my youngest son. Pete was the joy of my life. From the day he was born, Pete was someone very special. He made me smile every day and I thanked God that I had been blessed with such a wonderful gift. My three children meant the world to me and as a full time mother I enjoyed every minute that I spent with all of them. On the day that I began my job as a high school guidance counselor, Pete, who was ten, picked a bouquet of flowers from our garden for me. I had always given the children a small gift on the first day of school and told them how proud I was of them. Pete was doing the same thing for me. He was always a kind and thoughtful person who made people feel glad that they knew him. He brightened a room every time he entered it. He was always the center of attention; not because he asked for it, but because it seemed to come to him naturally. Pete was bright, funny, athletic, talented, a leader among his peers. I was proud of his accomplishments and prouder still of the man he was becoming.
Then one day the unthinkable happened - he died.

Pete had gone to Florida on Spring Break with some of his friends. On a cold and overcast day they decided to explore some of the shops along the beach. All week they had seen ads and banners promoting herbal supplements of all kinds. They went into one of the shops and decided to try one. It was all natural, safe, harmless, the store clerk said that she and her friends take 10 or 12 pills at a time and feel great, it gave them lots of energy! The boys tried it. Pete took somewhere between 4 and 8 pills and almost immediately began to feel strange. His heart rate was faster, he felt tingly, hot all over, had a pounding headache. He took a shower but it didn't help. He told the other boys to go out, that he would lie down for awhile until he felt better and would join them later. The last time his friends saw him alive he was sitting on the edge of the bed reading the label on the box. What had he taken? What was wrong? What should he do? There was no help on that box.

It took weeks, months for us to understand what happened to our beautiful, wonderful, healthy son. We still really don't understand. Perhaps we never will. But at

least now we do know the facts. Pete died because a company cared much more about profits than about lives. Pete died because he had an unfortunate chance encounter with Ultimate Xphoria. The maufacturers of this product have admitted that they are not sure how many or which additional herbs were in each batch. They claim not to know where the Ma huang came from, which part of the plant was used, the time of year it was harvested, how strong the concentration was. They didn't know or perhaps didn't care but my son died because Ultimate Xphoria was improperly manufactured and marketed towards young people. A number of ingredients in this product posed a risk to Pete or any other healthy individual. Combined they caused an insurmountable risk of harm. I know that there is a great deal of information in publications or on the internet that dispute these truths. I have read them myself. But, I have a copy of Pete's autopsy, something no mother should ever have to see, and it shows beyond a shadow of a doubt that there was nothing in Pete's system besides the ingredients in this product. He had been on spring break with his friends but there was no evidence of any drugs or alcohol, nothing but the lethal herbal supplement that he bought over the counter in a little shop on the beach.

Ephedrine is a drug. It has been a drug for over 5,000 years. No amout of legislation will make it a food. Proponents of ephedrine containing supplements like to say that the Chinese have used it for centuries. They have, through practitioners who prescribe it as a part of their traditional medicine, not for weight loss or as an energy boost.

Scientists have agreed on what ephedrine does; dilates bronchial muscles, contracts nasal mucosa, raises blood pressure, and acts as a cardiac stimulator. Although there may be some disagreement as to a safe limit of ephedrine, I do not dispute that in proper hands ephedrine can be appropriate and safe. However, the Dietary Supplement Health and Education Act of 1994 has allowed irresponsible persons to contaminate the market place with false claims and dangerous marketing. I doubt it was the intention of this governmental body to allow people like those who caused my son's death to get rich at the expense of America's youth. I fully understand that there are many people and certainly many manufacturers making millions of dollars from these products who don't want to hear any of this. But I would hope that my government would want to hear this. Filing an adverse event report was our vehicle to the truth. I did this in honor of my son Peter Charles Schlendorf.

Mr. BURTON. Ms. Michal.

Ms. MICHAL. Mr. Chairman and members of the committee, my name is Barbara Michal of Novi, MI, founder of the nonprofit National Coalition Halt Ephedrine Abuse Today. I am here today at my own personal expense, and I am deeply grateful for you allowing me to testify today.

My keen interest in the ephedrine regulation issue came about through a parent's deepest terror, the death of a child. On March 14, 1997, ephedrine killed my 24-year-old son Kristopher.

Since that time, I have been researching ephedrine; and I am appalled at how much information is available as to the serious dangers of this powerful cardiovascular and central nervous system stimulant and equally appalled at the lack of strict regulation of this drug.

Some members of the dietary supplement industry with their huge profits and their powerful lobbyists have mounted a concerted campaign to discredit the work of the FDA in gathering adverse event reports and in promulgating proposed ephedrine controls rules. Their motivation is to protect their profits, not the safety of the citizens of the United States.

Mainstream drug companies not only welcome adverse event reports, they have physicians and pharmacologists on staff to review and evaluate each adverse event report. With prescription and mainstream over-the-counter drugs, physicians and other healthcare practitioners know to report adverse events to the FDA.

However, the unregulated dietary supplement industry is another story all together. There is no industry-wide adverse event reporting procedure. Product labels generally do not carry 800 numbers for consumer use in reporting adverse events.

In general, the public is unaware that the FDA wants to receive adverse event reports on dietary supplements, and I strongly doubt that the dietary supplement manufacturers have physicians and pharmacologists on staff to evaluate what adverse event reports they do receive.

The industry disputes the validity of the data base of the FDA, yet they are not required to submit reports to it. Now they come to you complaining that the FDA adverse event reporting system is seriously deficient, the data base is suspect and the FDA has not used sound scientific studies upon which to base their proposed ephedrine control rules.

I respectfully ask whether the dietary supplement industry has submitted even one peer-reviewed, sound scientific study to prove the safety of their ephedrine-laced products in humans. They are bashing the science and data of the FDA because they have nothing of substance to support their position.

They also use the Chicken Little argument, the sky is falling. They claim that strict regulation of ephedrine will destroy the dietary supplement industry. This argument is preposterous on its face. Some dietary supplement manufacturers have recognized the serious dangers and potential liability of this amphetamine analog and have already removed it from their products; and those products are selling quite well, thank you.

My organization, Halt Ephedrine Abuse Today, is conducting a survey of ephedrine use on the Internet. As of April 30, 1999, with 227 people reporting, 48 percent report addiction.

Of those reporting using dietary supplement products as opposed to synthetic ephedrine products, 28 percent, over one-fourth report addiction. Among other adverse reactions, we have had reports of psychosis, stroke, cardiac arrythmia, kidney damage, nerve damage, heart attack, and death.

Contrary to the staffing problems with the FDA not being able to followup on these reports, I have spoken personally with many of these people after they have contacted me through the Internet. We have received an additional 85 responses since the end of April. They have not yet been collated.

This report is not scientific. It has not been reviewed by a licensed medical professional. It is purely the voices of American citizens detailing the adverse event reactions and injuries they have experienced. And this is just the tip of the iceberg.

My organization is hearing only from people with Internet access and who are actively seeking information on ephedrine; and of those, very few have reported their experiences to the FDA, and some even say, I didn't know I should.

Comparatively, the FDA already has in place a centralized reporting system where both private citizens and health-care professionals can report adverse reactions. If the industry has a problem with the reporting system and data collected, they should be working directly with the FDA to suggest improvements, which I have heard today they are doing, which I am very pleased with.

They should not be bringing their crusade to Congress in an effort to tar and feather the FDA without being sure that they provide constructive input as to how to fix the alleged deficiencies.

Regarding the industry's argument that the FDA has no legitimate science upon which to base their proposed ephedrine control rules, I respectfully refer the committee to the bibliography at the end of the June 2, 1997, proposed rules as published in the Federal Register.

Along with my written statement that I submitted, I included a bibliography of medical journal articles that I have collected. The proof is out there. The fire storm the industry is trying to ignite against the FDA serves only as smoke and mirrors to divert the focus from the real issue: Is ephedrine a threat to the health of the citizens of the United States? Yes.

Is the industry taking responsibility for seeking out and collecting adverse event reports to learn the truth? No. Does ephedrine need to be strictly regulated? Yes.

I sincerely thank you for this opportunity to be heard. The playing field in this controversy is far from level. We ephedrine victims and our families don't have millions of dollars in corporate profits to spend. We don't have powerful lobbyists with political connections. We don't have paid professionals whose job it is to be aware of and attend every hearing and committee meeting.

We are members of the general public; and we have a voice, too.

Thank you, Mr. Chairman and members of the committee, for hearing that voice.

Mr. BURTON. Well, thank you, Ms. Michal. We appreciate your comments.

[The prepared statement of Ms. Michal follows:]

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May 26, 1999

VIA FACSIMILE TRANSMISSION

Hon. Dan Burton, Chair
Government Reform Committee
United States House of Representatives
511 Ford House Office Building
Washington, D.C. 20515

Dear Representative Burton:

Please accept this letter as my written comment in preparation for the Committee hearing tomorrow, May 27, 1999, regarding the adverse event reporting system of the Food and Drug Administration, and specifically relating to ephedrine in dietary supplements.

My keen interest in the ephedrine issue arises out of a parent's deepest terror -- the death of a child. On March 14, 1997, ephedrine killed my 24 year old son, Kristopher. Since that time, I have been researching ephedrine and am appalled at how much information is available as to the extreme dangers of this powerful central nervous system and cardiovascular stimulant. As a result of all that I have learned, I formed a non-profit national coalition, Halt Ephedrine Abuse Today, whose mission is to educate the public about the dangers of ephedrine, to assist ephedrine victims and their families, and to promote reporting of adverse reactions to proper authorities and encourage scientific/medical studies regarding ephedrine and its effects on human health.

The dietary supplement industry with their massive profits and powerful lobbyists have mounted a concerted campaign to discredit the work of the FDA in gathering adverse event reports and in promulating proposed ephedrine control rules. Their motivation is to protect their profits, not the safety of the citizens of the United States. Mainstream drug companies not only welcome adverse event reports, they have physicians and pharmacologists on staff to receive and evaluate each adverse event report. If their data shows that their product is dangerous, they remove it from the market. With prescription and mainstream over-the-counter drugs, physicians and other health care practitioners know to report adverse reactions to the FDA MedWatch reporting system. However, the unregulated dietary supplement industry is another story altogether.

It appears that the dietary supplement industry has no such commitment to the safety of their products. There is no reporting procedure established by the industry; product labels generally do not carry 800 numbers for consumer use in reporting adverse events; the general

public is unaware that the FDA is interested in reports on dietary supplements; and I strongly doubt that any of the dietary supplement manufacturers have physicians and pharmacologists on staff to evaluate adverse event reports they may receive despite the difficulty the general public would have in trying to find out how to report them.

The industry has left that job to the FDA. Now, they come to you complaining that the FDA adverse event reporting system is seriously deficient, the database is suspect, and the FDA has not used sound scientific studies upon which to base their proposed ephedrine control rules. I respectfully ask whether the dietary supplement industry has submitted *even one* peer-reviewed sound scientific study to prove the safety of their ephedrine-laced products in humans? The tactic they are using is nothing more than bashing the science and data of the FDA because they have nothing of substance to support their position. They also use the "Chicken Little" argument -- "the sky is falling". They claim that strict regulation of ephedrine will destroy the dietary supplement industry. This argument is preposterous on its face. Some dietary supplement manufacturers have recognized the serious dangers and potential liability of ephedrine and have already removed it from their products. Those products are selling just fine, thank you.

I have enclosed for your review a compilation of adverse event reports my organization is collecting through a survey on the Internet regarding ephedrine use. As of April 30, 1999, with 227 people reporting, 48% report addiction; among other adverse reactions, we have had reports of psychosis, stroke, cardiac arrhythmia, kidney damage, and death. We have an additional 85 responses that have not yet been collated. This report is not scientific; it has not been reviewed by a licensed medical professional; it is purely the voice of the citizens of the United States detailing the adverse reactions and injuries they have experienced. Can the dietary supplement industry present any such compilation of citizen reports covering a multitude of products in one report? Do they have a centralized reporting system? And the reports my organization are getting are the tip of the iceberg. We are hearing from only those who have Internet access and are actively seeking information about ephedrine.

Comparatively, the FDA also has a centralized reporting system. The mechanism is already in place. If the industry has a problem with the reporting system and the data collected, they should work directly with the FDA to suggest improvements, not bring their crusade to Congress in an effort to tar and feather the FDA with no constructive input as to how to "fix" the alleged deficiencies, and with no formal proposal to establish their own reporting system.

Regarding the industry's argument that the FDA has no legitimate science upon which to base their proposed ephedrine control rules, I respectfully refer the Committee to the bibliography at the end of the June 2, 1997 proposed rules as published in the Federal Register. I also refer the Committee to the attach bibliography of medical journal articles I have collected. Is there any question that ephedrine is dangerous? No. Does ephedrine need to be strictly regulated? Yes.

Hon. Dan Burton
Government Reform Committee
United States House of Representatives
May 26, 1999
Page 3

I am anxious for the opportunity to testify in person at the Committee hearing tomorrow. I am a private citizen, not a paid lobbyist. The cost to me personally to come and testify is great; the information I can offer the Committee in personal testimony is important. It appears that four industry representatives/lobbyists are scheduled to testify, and two private citizens representing the other side of the story. Under the principle of "government of the people, by the people and for the people", the playing field needs to be level. Those of us who support the FDA and seek strict regulation of ephedrine are at a tremendous disadvantage from the first step -- we do not possess hundreds of millions of dollars in profits and we have no hired lobbyists. We are private citizens who need the opportunity to speak to our government representatives, and be present at the hearing for the committee members to question us, if they desire.

Thank you for your time and consideration of this comment.

Sincerely,

Barbara J. Michal

Barbara J. Michal

:bjm
enclosures

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NUMBER OF CONTACTS: 227 April 30, 1999

Male 100
Female 127

Youngest 16 Years
Oldest 62 years

Breakdown by age:
16-20: 44 contacts
21-25: 60 contacts
26-30: 61 contacts
31-35: 28 contacts
36-40: 15 contacts
41-45: 9 contacts
46+: 5 contacts
Unknown age: 5 contacts

CONTACTS REPORTING ADDICTION/DEPENDENCE: 110 (48%)

Male 48
Female 62

CONTACTS REPORTING DOSAGE RUN-UP: 107 (47%)

REPORTED ADVERSE REACTIONS:

Rapid Heart Beat	166	(73%)
Nervousness/tremors	153	(67%)
Insomnia	137	(60%)
Headaches	101	(44%)
Stomach Upset	95	(42%)
Irregular Heartbeat	88	(39%)
Chest Pain	76	(33%)
Shortness of Breath	75	(33%)
Body Aches	73	(32%)
Paranoia	60	(26%)
Difficult Urination	54	(24%)
Hallucinations	31	(14%)
Blackouts	23	(10%)
Seizures	8	(4%)

USING PRIMARILY CHEMICAL EPHEDRINE PRODUCTS: 114
Reporting Addiction: 78 (68%)
USING PRIMARILY HERBAL EPHEDRINE PRODUCTS: 113
Reporting Addiction: 32 (28%)

HALT EPHEDRINE ABUSE TODAY

Tabulation of Contacts through April, 30, 1999

DATA	1	2	3	4	5	6	7	8	9	10
Age	06/22/72 26	08/18/70 28	07/24/73 25		07/26/76 22	11/21/75 23	04/11/68 30	12/25/68 30	11/6/71 27	2/12/72 26
Gender	Male	Female	Male	Female	Female	Male	Female	Female	Female	Female
Marital Status	Married	Single	Married		Single	Single	Married	Married	Single	Single
Location			Maryland		Mississippi	Minnesota	Kansas	Georgia	California	
Addicted/Dependent	X		X		X		X	X	X	X
Rapid Heart Beat	X	X	X		X		X	X	X	X
Blackouts					X				X	
Difficult Urination					X			X	X	X
Irregular Heartbeat	X		X		X				X	X
Seizures			X		X				X	
Body Aches									X	X
Nervousness/Tremors	X				X			X	X	X
Paranoia	X				X				X	X
Chest Pain	X		X		X		X	X	X	X
Insomnia	X	X	X	X	X		X	X	X	X
Hallucinations			X		X				X	X
Headaches	X		X		X				X	X
Stomach Upset	X				X		X		X	X
Shortness of Breath	X				X				X	X
Other				Platelets Plummeted					Blood in Stool UTI	
Product	Ephedrine Plus	Revive, Black Cross	MaxAlert	Metabolife	Mini-Thins, Ripped Fuel	Ephedrine Plus	Mini-Thins	Mini-Thins	Mini-Thins	ephedrine
Starting Amount/day (1 tab = 25 mg.)	1-2 tabs	40 tabs	1 tab		20-30 tabs	1 tab	1 tab	30 tabs	3-12 tabs	9-15 tabs
Current or Ending Amount/day	5-10 tabs	40 tabs	6 tabs		60-100 tabs	1 tab	6 tabs	60 tabs	3-12 tabs	36-48 tabs
Length of Use	Unknown	2 years	6 years		4 years	1 year	8 years	9 years	5 years	7 years

Age	2/4/79 19	12/14/70 28	3/12/70 28	11/17/67 31	/2/75 23	9/5/76 22	11/22/72 26	7/29/68 30	9/20/67 31	/14/76 20
Gender	Male	Female	Female	Male	Male	Male	Female	Female	Male	Female
Marital Status	Single	Married	Single	Married	Single	Single	Married	Married	Single	Single
Location	Texas	Minnesota	Florida	Virginia	Canada	Pennsylvania	Georgia		South Africa	
Addicted/Dependent	X		X			X	X		X	
Rapid Heart Beat	X		X		X	X	X	X	X	X
Blackouts										
Difficult Urination				X		X			X	
Irregular Heartbeat			X		X		X		X	
Seizures										
Body Aches	X						X		X	X
Nervousness/Tremors	X	X	X		X	X	X	X	X	X
Paranoia	X					X			X	
Chest Pain	X						X		X	
Insomnia	X				X	X	X	X	X	
Hallucinations						X			X	
Headaches	X					X	X	X	X	
Stomach Upset	X					X	X			
Shortness of Breath			X		X		X		X	
Other			Dry mouth; Mood swings			Psychosis-diag. schizo.			Psychosis-diag. schizo.	
Product	Diet Max	Efedrin	Metabolife	Max Alert	thermogenic products	Max Alert	Two-Way Heads Up	Mini-Thins	Thinz Sudafed Nobess	ma huang
Starting Amount/day (1 tab = 25 mg.)	1 pill (mg?)	2 tabs	2 pills (mg?)	1 tab	24 mg.	"several"	6 tabs	2 tabs	12 pills (mg?)	1 pill (mg?)
Current or Ending Amount/day (1 tab = 25 mg.)	4 pills (mg?)	2 tabs	6-7 pills (mg?)	18 tabs	24 mg.	7 tabs	30 tabs	5 tabs	2 pills (mg?)	1 pill (mg?)
Length of Use	1 year	10 years	months	3 years	2 years	1 year	7 years	? years	? years	2 years

DATA	21	22	23	24	25	26	27	28	29	30
Age	10/20/67 31	3/22/63 35	11/13/73 26	5/13/80 18	8/30/70 28	8/5/70 28	7/18/74 24	7/11/61 37	7/14/73 25	3/7/57 41
Gender	Female	Female	Female	Male	Female	Female	Male	Female	Female	Female
Marital Status	Married	Married	Single	Single	Single	Married	Single	Single	Married	Married
Location	Georgia	Michigan	Canada		Georgia	Illinois	Canada	Nevada	Texas	California
Addicted/Dependent	X	X			X	X	X			
Rapid Heart Beat	X	X	X	X	X	X	X		X	
Blackouts										
Difficult Urination										
Irregular Heartbeat	X					X	X			
Seizures										
Body Aches	X					X				
Nervousness/Tremors	X	X	X	X	X	X			X	
Paranoia						X			X	
Chest Pain	X		X		X	X	X			
Insomnia	X	X	X	X	X	X				
Hallucinations				X						
Headaches	X		X		X	X			X	
Stomach Upset			X		X	X				X
Shortness of Breath			X		X	X				
Other									emotional instability	
Product	Two-Way Heads Up	Primatene	Diet Pep Diet Fuel Proenzi 99	Efedrin	Mini-Thins Heads Up	pseudo-ephedrine	ephedrine HCL	Ripped Fuel	Go Power Mini-Thins	Herbalife
Starting Amount/day (1 tab = 25 mg.)	2 tabs	6-12 pills (12.5 mg. ea)	2-4 pills (8 mg. ea)	2 tabs	4 6 tabs	5 pills (60 mg. ea)	1 tab	2 pills (mg?)	1 tab	
Current or Ending Amount/day (1 tab = 25 mg.)	12-22 tabs	36 pills (12.5 mg. ea)	3-4 pills (8 mg. ea)	2 tabs	12-16 tabs	65 pills (60 mg. ea)	6 tabs	2 pills (mg?)	5-6 at a time several times a day	
Length of Use	9 years	7 years	7 years	1 year	9 years	10 years	3 years	months	8 years	months

DATA	31	32	33	34	35	36	37	38	39	40
Age	8/26/66 32	8/26/63 35	11/16/68 30	4/2/72 26	8/22/73 25	9/18/76 22	7/23/79 19	1/6/73 25	4/28/74 24	12/24/75 23
Gender	Female	Female	Male	Female	Female	Male	Male	Female	Male	Male
Marital Status	Married	Married	Single	Married	Single	Single	Single	Single	Single	Single
Location	Oklahoma	Wisconsin	Georgia	Hawaii	Canada	Michigan	Illinois	Alabama	Canada	California
Addicted/Dependent	X						X	X		
Rapid Heart Beat		X	X	X	X	X		X	X	X
Blackouts							X			
Difficult Urination						X			X	X
Irregular Heartbeat		X	X			X	X			X
Seizures										
Body Aches		X					X	X		X
Nervous ness/Tremors	X	X	X		X	X	X	X		
Paranoia								X		
Chest Pain		X				X	X	X		
Insomnia			X		X	X		X		X
Hallucinations								X		
Headaches	X	X					X	X		
Stomach Upset					X	X				
Shortness of Breath		X		X		X		X		
Other	Memory loss, difficulty with concentration	Elevated BP	Hospitalized-card. arrhyth and elevated BP	Hair loss				emotional instability, anger		temporary penis shrinkage
Product	EPH 833	Herbal Phen	Metabolife	Xenadrine RFA-1	Thermadrene	Mini-Thins	Ripped Fuel Black Cross	herbal products, Chromium Herbal 5000	Mini-Thins, Thermadrene	Dimetadrine
Starting Amount/day (1 tab = 25 mg.)	3-4 pills (mg?)				1 pill (mg?)	8 tabs	6 pills (mg?)	rec. dosage	2-4 tabs sev. times/week	3 pills (mg?)
Current or Ending Amount/day (1 tab = 25 mg.)	3-4 pills (mg?)				1 pill (mg?)	8 tabs	3 pills (mg?)	rec. dosage	occasionally 2-3 tabs	7-11 pills (mg?)
Length of Use	1 year	2 weeks	months	months	months	8 years	1 year	7-8 years	4-5 years	1 year

DATA	41	42	43	44	45	46	47	48	49	50
Age	1/13/81 17	1/18/70 28	1/29/58 40	7/14/70 28	4/17/81 17	9/17/73 25	6/5/79 19	12/4/73 26	11/11/69 29	11/4/74 24
Gender	Female	Male	Female	Female	Female	Female	Male	Female	Male	Female
Marital Status	Single	Single	Married	Married	Single	Single	Single	Single	Married	Single
Location	Oregon	Georgia	Delaware	California			Illinois		Pennsylvania	Minnesota
Addicted/Dependent	X		X	X	X				X	X
Rapid Heart Beat	X		X		X		X		X	X
Blackouts	X									X
Difficult Urination									X	
Irregular Heartbeat	X			X	X					X
Seizures										X
Body Aches					X					X
Nervousness/Tremors	X		X	X	X		X		X	X
Paranoia	X				X					X
Chest Pain			X		X					X
Insomnia	X		X	X	X		X		X	X
Hallucinations										X
Headaches	X		X		X					X
Stomach Upset	X				X		X		X	X
Shortness of Breath	X		X		X					X
Other	suicidal feelings			card. arrhyth after stopped product	emotional instability					migraine; panic disorder
Product	diet pills allergy pills	ma huang	ephedra	Ultra Diet Pep; Diet Fuel	Diet Fuel	ma huang	ephedrine HCL	Ultra Citra Slim	Mini-Thins Ephedrine Plus	White Cross Metabolife Thermolift
Starting Amount/day (1 tab = 25 mg.)	1 pill (mg?)	2 pills (mg?)	1 pill (mg?)	2 pills (mg?)	9 pills (mg?)	30 mg.	"varies"	6 pills (mg?)	1 tab	100-150 mg.
Current or Ending Amount/day (1 tab = 25 mg.)	12 pills (mg?)	2 pills (mg?)	1 pill (mg?)	2 pills (mg?)	6 pills (mg?)	30 mg.	"varies"	6 pills (mg?)	6 tabs	50 mg.
Length of Use	1 year	2 years		3 years	2 years	months	3 years			3 years

DATA	51	52	53	54	55	56	57	58	59	60
Age	5/3/76 20	5/6/70 28	11/21/79 19	7/28/78 20	9/2/70 28	12/2/54 44	4/23/80 18	3/30/64 34	2/26/72 26	40
Gender	Female	Female	Female	Male	Male	Male	Male	Female	Female	Female
Marital Status	Single	Single	Single	Single	Single	Married	Single	Married	Single	Single
Location	England		Pennsylvania	Florida	Pennsylvania	California		Florida	Washington	California
Addicted/Dependent	X	X			X					
Rapid Heart Beat	X	X		X	X	X			X	X
Blackouts			X							
Difficult Urination	X	X			X					
Irregular Heartbeat	X	X		X	X					
Seizures										
Body Aches	X	X		X						
Nervousness/Tremors	X	X	X	X	X				X	
Paranoia	X			X	X					
Chest Pain	X			X						
Insomnia	X	X	X	X	X		X		X	
Hallucinations			X							
Headaches	X	X	X	X						
Stomach Upset	X	X			X					
Shortness of Breath	X				X				X	
Other		depression, emotional instability, hives, skin "crawling"	non-specific mental disturbances after stopped use	exfoliative dermatitis, muscle spasms	in-patient drug rehab					recovering drug addict - "speed"
Product	Ultimate Orange T6	Mini-Thins Two Way Max Alert	Diet Fuel	Mini-Thins Two Way Dystreme	Mini-Thins	Metabolife	herbal and chemical ephedrine	Nature's Chi Natural Trim	ma huang	Power Trim
Starting Amount/day (1 tab = 25 mg.)	350 mg.	2-4 tabs	9 pills (mg?)	1 tab	2 tabs		25-35 mg.	88 mg.	4 pills (mg?)	2 pills (mg?)
Current or Ending Amount/day (1 tab = 25 mg.)	1200 mg.	12-15 tabs	6 pills (mg?)		180 tabs		25 mg.	88 mg.	4 pills (mg?)	
Length of Use	3 years	8 years	1 year	2 years	7 years	1 year	months	days	days	took once

DATA	61	62	63	64	65	66	67	68	69	70
Age	1/7/75 23	11/7/77 21		11/12/70 28		7/4/81 17	6/23/81 17	6/25/74 24	6/22/53 45	12/13/74 24
Gender	Female	Male	Male	Male	Female	Female	Male	Female	Male	Male
Marital Status	Single	Single	Single	Single	Married	Single	Single	Married	Married	Single
Location		Canada	Florida	New Mexico	Texas	Kansas	Mississippi	Oklahoma	Florida	New York
Addicted/Dependent			X	X	X	X	X			X
Rapid Heart Beat		X	X	X	X	X	X	X	X	X
Blackouts							X			
Difficult Urination			X		X				X	
Irregular Heartbeat		X		X	X	X	X	X		
Seizures										
Body Aches			X		X			X		X
Nervousness/Tremors	X	X	X	X	X	X	X	X		X
Paranoia			X	X	X	X				
Chest Pain				X	X	X				X
Insomnia		X	X	X	X	X	X	X		X
Hallucinations					X					
Headaches		X	X	X	X		X	X		X
Stomach Upset	X		X		X	X		X		X
Shortness of Breath			X	X	X		X			
Other				weight gain, depression				former drug addict - "meth"		elevated BP
Product	Hydroxycut	Dymetadrine	Mini-Thins	Ephedrine Plus	Mini-Thins	MegaTrim 3000	Mini-Thins	Advantage AM-300	Mini-Thins	ECA stack Mini-Thins
Starting Amount/day (1 tab = 25 mg.)	4 pills (mg?)	200 mg.	2-4 tabs	1 tab	1 tab	2 pills (mg?)	4 tabs	2 pills (mg?)	4 tabs	100 mg.
Current or Ending Amount/day (1 tab = 25 mg.)	2 pills (mg?)	300 mg.	"high double digits/day"	4 tabs	25 tabs	2 pills (mg?)	6 tabs		6 tabs	150 mg.
Length of Use	weeks	4 years		7 years		months	3 years	took once	15 years	3 years

DATA	71	72	73	74	75	76	77	78	[illegible]	[illegible]
Age	7/19/74 24	6/25/74 24	11/21/54 44	01/03/77 22	01/01/78 20	03/24/76 22	05/21/65 33	01/28/74 25	08/15/67 31	[illegible]24/77 26
Gender	Female	Female	Female	Female	Male	Male	Female	Female	Male	Female
Marital Status	Single	Married	Divorced	Single	Single	Single	Divorced	Married	Married	Single
Location	New Jersey	Texas	Georgia	Texas		Canada		Minnesota	Wisconsin	Canada
Addicted/Dependent		X	X	X	X		X	X	X	
Rapid Heart Beat	X	X	X	X	X		X	X		X
Blackouts							X			
Difficult Urination										
Irregular Heartbeat			X	X	X		X	X		X
Seizures										
Body Aches		X	X	X			X	X		
Nervousness/Tremors	X		X	X	X		X	X	X	X
Paranoia			X	X			X			X
Chest Pain			X	X			X			X
Insomnia	X	X	X		X		X	X	X	
Hallucinations							X		X	
Headaches		X								
Stomach Upset	X	X	X	X	X		X		X	
Shortness of Breath			X	X			X		X	X
Other			Irrational Behavior; depression	Vision changes						Anxiety, Depression
Product	Mini-Thins	Mini-Thins	Mini-Thins Two Way	Dynamic Metabolic Booster	types found in gas stations	Diet Fuel	Diet Pep; Herbalife; Mini-Thins Two Way	Ephedrine Plus; ma huang; Mini-Thins	types found in gas stations	ephedrine
Starting Amount/day (1 tab = 25 mg.)	3 tabs	2-10 tabs	1-2 tabs	3 pills (mg?)	5 tabs	3 pills	100-150 mg.	1-2 tabs	1-2 tabs	2-3 tabs 3 to 5 times a week
Current or Ending Amount/day (1 tab = 25 mg.)	6 tabs	15-30 tabs	1-2.5 tabs	2 pills (mg?)	25 tabs	3 pills	600 mg.	3-7 tabs	75+ tabs	2 tabs 5 to 7 times a week
Length of Use	2 years	11 years	5 years	1 year	months	days	3 years	6 years	6 years	1 year

DATA	81	82	83	84	85	86	87	88	89	90
Age	12/06/68 30	10/02/73 25	11/10/72 28	09/08/79 19	09/28/72 26	04/17/65 33	05/21/62 36	11/07/82 18	09/20/77 21	06/02/51 47
Gender	Male	Male	Female	Female	Male	Female	Female	Male	Female	Female
Marital Status	Married	Married	Single	Single	Single	Married	Married	Single	Single	Married
Location	Iowa	Georgia	Pennsylvania		New York	England	Texas		Connecticut	New York
Addicted/Dependent	X		X	X				X	X	
Rapid Heart Beat	X		X		X	X		X	X	X
Blackouts									X	
Difficult Urination	X		X		X					
Irregular Heartbeat	X		X						X	
Seizures			X				X			
Body Aches	X			X	X			X		
Nervousness/Tremors	X	X	X		X	X			X	
Paranoia				X						
Chest Pain	X				X				X	
Insomnia	X	X			X	X		X	X	
Hallucinations				X		X		X	X	
Headaches	X		X	X	X			X	X	
Stomach Upset	X	X	X		X	X		X		
Shortness of Breath	X		X		X				X	
Other	Cranky						Stroke		Depression	Exacerbated Pre-Existing Panic Disorder
Product	Efedrin	Metabolift	Mini-Thins Black Cross	Two Way	Diet Fuel	Blue Ladies	Metabolifs	Up Your Gas Ultimate Orange	Thermadrene	ephedra
Starting Amount/day (1 tab = 25 mg.)	5-10 tabs	3 doses (mg?)	2-3 tabs	4-6 tabs	9 pills (mg?)	4-5 @ 50 mg.	4 pills (mg?)	500 mg. +	1 pill (mg?)	1 pill (mg?)
Current or Ending Amount/day (1 tab = 25 mg.)	200 tabs	3 doses (mg?)	15 tabs	4 tabs	9 pills (mg?)	16 @ 50 mg.	4 pills (mg?)	500 mg. +	2-3 pills (mg?)	1 pill (mg?)
Length of Use	12 years	months	2 years	2 years	months	1 year	months	4 years	1 year	3 days

DAT	91	92	93	94	95	96	97	98	99	100
Age	11/18/74 24	12/7/82 18	04/27/66 32	09/06/69 29	02/08/71 27	08/19/69 29	02/03/76 22	10/09/55 43	05/2690 18	06/11/66 32
Gender	Male	Male	Male	Female	Female	Female	Male	Female	Female	Male
Marital Status	Married	Single	Married	Married	Married	Married	Single	Married	Single	Married
Location	Pennsylvania		Georgia	California	Colorado		Wisconsin	Colorado		
Addicted/Dependent	X		X	X	X	X	X		X	
Rapid Heart Beat	X		X	X	X	X	X			
Blackouts			X							
Difficult Urination	X						X			
Irregular Heartbeat	X		X		X		X			
Seizures										
Body Aches	X		X		X					
Nervousness/Tremors	X		X		X		X		X	
Paranoia	X		X							
Chest Pain	X				X		X			
Insomnia	X		X		X		X		X	
Hallucinations										
Headaches	X		X		X				X	
Stomach Upset			X							
Shortness of Breath	X		X							
Other	Several trips to ER; dizziness		Impotence; short temper		Depression		Difficulty in speaking			ECA stack
Product	types found in gas stations	Thermadrene	Heads Up Mini-Thins Two Way	Dymetadrine	Suphedrine Ephedrine	Mini-Tabs	Efedrin Plus	Metabolic 2000	ThermoGenics Plus	Mini-Thins
Starting Amount/day (1 tab = 25 mg.)	4-5 tabs	2 pills (mg?)	2 tabs	1 pill (mg?)	4-5 pills (mg?)	2 pills (mg?)	3 tabs	68 mg.	3 pills (mg?)	3 tabs
Current or Ending Amount/day (1 tab = 25 mg.)	60 tabs	3 pills (mg?)	25 + tabs	1 pill (mg?)	8-10 pills (mg?)	5 pills (mg?)	30 tabs	34 mg	3 pills (mg?)	3 tabs
Length of Use	5 years	1 year	10 years	7 years	11 years	11 years	5 years	3 years	1 year	2 years

DATA	101	102	103	104	105	106	107	108	109	110
Age	5/11/75 23	7/7/71 27		11/20/80 18	12/9/63 35	5/25/77 21	1/26/77 22	8/13/75 23	1971 27	12/2/73 25
Gender	Female	Female	Female	Male	Female	Male	Male	Male	Female	Male
Marital Status	Single	Single		Single	Married	Single	Single	Married	Married	Married
Location	Virginia	Florida	Missouri		Georgia	Canada	Oklahoma	Kentucky		Texas
Addicted/Dependent					X			X		X
Rapid Heart Beat		X			X	X	X	X		X
Blackouts										
Difficult Urination										X
Irregular Heartbeat		X						X		X
Seizures										
Body Aches		X						X		X
Nervousness/Tremors		X			X			X		X
Paranoia		X	X					X		X
Chest Pain		X			X			X		X
Insomnia		X			X			X	X	X
Hallucinations								X		
Headaches	X			X				X		X
Stomach Upset		X						X		X
Shortness of Breath		X			X			X		X
Other			Hospitalized - hypertension & paranoia					Memory loss		
Product	Ripped Fuel, Mini Tabs	Up Your Gas	Metabolife	Xenadrene	Heads Up	Ephedrine HCL	Metaform Metacuts	Mini Thin Two-Way	Metabolife	Mini-Thin Two-Way
Starting Amount/day 1 tab = 25 mg.	"recommended dose"	1 pill (mg?)	?	4 pills (mg?)	5-10 pills (mg?)	1 pill (mg?)	20 mg.	1 tab	6-8 pills (mg?)	5 tabs
Current/Ending Amount/day 1 tab = 25 mg.	"recommended dose"	2 pills (mg?)	?	3 pills (mg?)	Up to 200 pills (mg?)	1 pill (mg?)	20 mg.	50 tabs	6-8 pills (mg?)	60-95 tabs
Length of Use	months	1 year	?	weeks	13 years	months	1 year	8 years	months	5 years

DATA	111	112	113	114	115	116	117	118	119	120
Age	2/28/74 24	21	6/13/63 35	1/3/66 33	4/19/68 30	11/28/69 29	2/29/80 19	6/14/78 20	6/3/81 17	2/12/76 23
Gender	Male	Female	Female	Male	Male	Female	Male	Female	Female	Male
Marital Status	Single	Married	Divorced	Married	Single	Single	Single	Single	Single	Single
Location			Texas	California	Louisiana		Canada		Georgia	Delaware
Addicted/Dependent			X		X			X	X	
Rapid Heart Beat			X		X		X	X	X	X
Blackouts			X							
Difficult Urination			X		X					X
Irregular Heartbeat			X		X				X	X
Seizures										
Body Aches			X		X					
Nervousness/Tremors			X		X			X	X	X
Paranoia			X		X					X
Chest Pain			X		X					
Insomnia	X	X	X		X	X	X			X
Hallucinations			X							
Headaches		X	X		X	X			X	
Stomach Upset	X		X		X	X	X		X	X
Shortness of Breath			X		X	X	X			
Other			Kidney damage			Sinus problem, constipation				
Product	Thermadrene	Prozazi 99	Mini-Thin, White Cross, Xelence, Two-Way, Pink Hearts	Omnitrition	EPH 883, Herbal Dynomight, Ripped Fuel, Mini-Thin	Thermo-Genics Plus	Ripped Fuel Thermadrine	Max Alert	Ma huang	Efedrin
Starting Amount/day 1 tab = 25 mg.	1 pill (mg?)	Recommended amount	2 (mg?)	1 packet (mg?)	3 caps (mg?)	3-6 caps (mg?)	24 mg.	50 mg.	3 caps (mg?)	4 tabs (mg?)
Current/Ending Amount/day 1 tab = 25 mg.	2 pills (mg?)	Recommended amount	?	1 packet (mg?)	10+ caps (mg?)	6 caps (mg?)	100 mg.	375 mg	2 caps (mg?)	4 tabs (mg?)
Length of Use	3 years	weeks?	1 year	weeks	2 years	months	1 year	?	months	months

DATA	121	122	123	124	125	126	127	128	129	130
Age	6/5/77 21	3/16/80 19	11/13/53 45	1966 33	7/20/75 23	2/27/80 19	6/7/64 34	11/6/79 19	1/7/75 24	9/14/62 36
Gender	Female	Female	Male	Male	Male	Male	Male	Female	Female	Female
Marital Status	Single	Single	Married		Single	Single	Single	Single	Single	Married
Location	Canada		Texas	Pennsylvania	Chile	Georgia		Illinois	Michigan	Tennessee
Addicted/Dependent	X						X			
Rapid Heart Beat	X		X	X	X		X		X	
Blackouts										
Difficult Urination										
Irregular Heartbeat										
Seizures										
Body Aches								X		
Nervousness/Tremors	X		X	X	X		X		X	
Paranoia	X									
Chest Pain				X			X	X		
Insomnia					X			X		
Hallucinations										
Headaches					X	X	X	X	X	X
Stomach Upset							X			
Shortness of Breath	X									
Other			heart attack						irritable	
Product	Proenzi 99	Proenzi 99	Ripped Fuel	Max Ten	Ephedrine + caffeine	Two Way	ephedrine + guaifenesin	Thermolift	Metabolife	Powertrim
Starting Amount/day 1 tab = 25 mg.	2 caps (mg?)	24 mg.	2 caps (mg?)	4 tabs	200 mg.	75 mg.	3 tabs	1 cap (mg?)	2 caps (mg?)	70 mg.
Current/Ending Amount/day 1 tab = 25 mg.	3-4 caps (mg?)	24 mg.	2 caps (mg?)	3-4 tabs	200 mg.	75 mg	21 tabs	2 caps (mg?)	2-3 caps (mg?)	70 mg
Length of Use	months	months	months	months	2 years		12 years	weeks	months	weeks

DATA	131	132	133	134	135	136	137	138	139	140
Age	8/4/69 29	5/20/76 22	4/8/71 27	1/26/62 37	/30/75 23	12/1/77 21	11/4/76 22	9/7/78 20	7/4/58 40	/9/72 28
Gender	Female	Female	Male	Female	Female	Male	Female	Male	Female	Female
Marital Status	Married	Single	Single	Married	Married	Single	Single	Single	Married	Single
Location	California	Canada	Maryland	Texas	Washington			New York	Indiana	
Addicted/Dependent		X	X	X	X	X		X	X	X
Rapid Heart Beat	X	X	X	X	X	X	X	X	X	X
Blackouts			X							
Difficult Urination		X	X			X			X	
Irregular Heartbeat			X			X	X	X	X	
Seizures										
Body Aches		X	X				X		X	
Nervousness/Tremors	X	X	X	X		X	X	X	X	X
Paranoia			X			X	X			
Chest Pain		X	X	X				X	X	
Insomnia		X	X			X	X	X	X	
Hallucinations						X				
Headaches		X	X	X				X	X	
Stomach Upset			X	X		X		X	X	X
Shortness of Breath		X	X				X	X	X	
Other			Chills, Dry mouth							Kidney stones
Product	Ma huang	Ma huang	Max Alert	Ephedrine	Java Trim Extra	Ballistics	Thermoslim	Ma huang	Mini Thins Max Alert	Mini Thins
Starting Amount (1 tab = 25 mg.)	2 caps (mg?)	1-2 caps (mg?)	100 mg.	150 mg.	20 mg.	3 caps (mg?)	3 caps (mg?)	25 mg.	10 tabs	25 mg
Current/Ending Amount (1 tab = 25 mg.)		2-4 caps (mg?)	1200 mg.	50 mg.	40 mg.	12 caps (mg?)	3 caps (mg?)	150-175 mg	40-60 tabs	100-125 mg.
Length of Use	Once	1 year	7 years	3 years	months	1 year	weeks	4 years	10 years	4 years

DATA	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Age	2/17/60 39	2/3/79 20	11/25/70 28	11/21/72 26	5/23/64 34	6/1/61 37	3/9/37 62	5/1/68 30	9/25/74 24	2/2/75 24
Gender	Male	Male	Male	Female	Male	Female	Male	Female	Female	Male
Marital Status	Married	Single	Married	Single	Divorced	Single		Single	Single	Single
Location	California	Canada	Louisiana			Michigan	California		Michigan	England
Addicted/Dependent	X		X			X		X		
Rapid Heart Beat	X		X	X	X	X		X	X	
Blackouts						X				
Difficult Urination			X			X			X	
Irregular Heartbeat				X		X				
Seizures										
Body Aches			X	X		X			X	
Nervousness/Tremors		X		X	X	X		X	X	
Paranoia		X				X		X		
Chest Pain			X	X		X				
Insomnia		X	X	X	X	X		X	X	
Hallucinations					X	X				
Headaches			X	X		X			X	
Stomach Upset			X	X		X				
Shortness of Breath		X		X				X	X	
Other										
Product	EPH 833	Thermadrene	Max Alert Mini-Thin	Two Way	Slim & Trim	Max Alert Thin Tabs	ephedra	ephedrine hcl	E'Ota Amp II Pro Drops	Metaform Metacuts
Starting Amount (1 tab = 25 mg.)	1 cap (mg?)	2 caps (mg?)	3 tabs	2-6 tabs	3 caps (mg?)	2 tabs	40 mg.	25-50 mg.	30 mg.	4 caps (mg?)
Current/Ending Amount (1 tab = 25 mg.)	1 cap (mg?)	2 caps (mg?)	30 tabs	5-6 tabs	3 caps (mg?)	18-20 tabs	60 mg.	200 mg.	30 mg.	?
Length of Use	2 months	2 years	6 years	months	days	9 years	1 year	10 years	4 weeks	1 year

DATA	151	152	153	154	155	156	157	158	159	160
Age	5/30/65 33	11/4/81 18	6/25/69 29	5/1/73 25	4/13/75 23	4/1/65 33	8/31/68 30	8/5/74 24	2/28/63 36	28
Gender	Female	Male	Female	Female	Female	Male	Male	Female	Male	Male
Marital Status	Single	Single	Married	Single	Single	Married	Married	Single	Married	Married
Location	North Carolina	Minnesota	North Carolina	Canada	California	Ohio	Georgia	Texas	New Jersey	Michigan
Addicted/Dependent	X					X	X			X
Rapid Heart Beat	X	X	X	X			X	X		X
Blackouts	X						X			
Difficult Urination	X					X	X			X
Irregular Heartbeat	X					X	X	X		X
Seizures	X									
Body Aches	X		X				X			X
Nervousness/Tremors	X					X	X	X		X
Paranoia	X					X	X			
Chest Pain	X						X			X
Insomnia	X			X	X		X	X		X
Hallucinations	X									
Headaches	X	X				X				X
Stomach Upset	X	X				X	X	X		X
Shortness of Breath	X									
Other					Numbness in arm	Panic attacks		Hand tremors for 5 years		Kidney Stones
Product	Mini-Thin	Ripped Fuel Ephedra 850	Natural Trim	Ephedrine/ caffeine/ aspirin stack	Xenadrine	Mini-Thin	Mini-Thin Two Way	Mini Thin Metabolife	Dymetadrine	Mini-Thin
Starting Amount (1 tab = 25 mg.)		4 caps (mg?)	4 caps (mg?)		4 caps (mg?)	2 tabs	200 mg.		50-100 mg.	120 tabs/day
Current/Ending Amount (1 tab = 25 mg.)	2500 mg.		4 caps (mg?)		4 caps (mg?)	2 tabs	1500 + mg.		50-100 mg	60 tabs/day
Length of Use	6 years	3 years	weeks	6 months	months	years	13 years	over the past 5 years off and on	6 years	8 years

DATA	161	162	163	164	165	166	167	168	169	170
Age	4/23/61 37	10/1/73 25	4/29/70 28	10/10/76 22	43	5/1/79 20	11/23/75 23	12/14/72 26	12/19/78 20	10/16/79 19
Gender	Female	Male	Female	Male	Male	Female	Male	Male	Male	Female
Marital Status	Married	Married	Single	Single	Married	Single	Single	Single	Single	Single
Location		North Carolina	Texas	Indiana	Tennessee		Kentucky	Mass.	Missouri	
Addicted/Dependent		X		X	X	X				
Rapid Heart Beat	X	X	X	X	X	X		X	X	X
Blackouts					X					
Difficult Urination		X			X			X		
Irregular Heartbeat	X	X	X	X	X					X
Seizures										
Body Aches		X			X					
Nervousness/Tremors	X	X	X	X	X	X			X	X
Paranoia		X			X	X				X
Chest Pain		X	X	X	X					
Insomnia		X	X	X	X	X				X
Hallucinations		X								
Headaches	X	X		X	X	X				
Stomach Upset		X		X	X					X
Shortness of Breath		X	X	X	X					X
Other		Kidney stones			Collapsed & died 11/97				Edgy at night	
Product	Metabolic Nutrition	Mini-Thin Max Alert	Metabolife	Mini-Thin Max Alert Ripped Fuel	Ripped Fuel	Mini-Thin Two-Way	Ripped Fuel	Mini-Thin	Ripped Fuel	Bio-X
Starting Amount (1 tab = 25 mg.)	2 packets (mg?)	6 tabs	4 caps (mg?)	4-5 tabs	6 caps (mg?)	1-2 tabs	3 caps (mg?)	10 tabs	4 caps (mg?)	1-3 caps (mg?)
Current/Ending Amount (1 tab = 25 mg.)	2 packets (mg?)	60 tabs	2 caps (mg?)	13-15 tabs	6 caps (mg?)	5-6 tabs	4 caps (mg?)	2-4 tabs	6 caps (mg?)	
Length of Use	months	2 years	2 years	3 years	?	3 years	months	2 years	1 year	1 year

DATA	171	172	173	174	175	176	177	178	179	180
Age	9/6/70 28	9/19/69 29	6/17/72 26	1966 33	3/31/76 22	7/22/73 25	6/20/79 19	12/10/40 58	12/9/64 34	5/22/72 26
Gender	Male	Female	Male	Female	Male	Female	Male	Male	Female	Female
Marital Status	Married	Divorced	Single	Married	Single	Married	Married	Married	Married	Divorced
Location	Alabama		Oregon	Oregon	India			Maryland	Texas	
Addicted/Dependent	X	X			X	X				
Rapid Heart Beat		X		X	X		X			X
Blackouts										
Difficult Urination	X									
Irregular Heart Beat							X			X
Seizures					X					
Body Aches	X								X	X
Nervousness/Tremors	X	X		X	X			X		X
Paranoia										X
Chest Pain										X
Insomnia	X	X	X		X		X		X	X
Hallucinations										
Headaches		X					X			X
Stomach Upset	X				X					X
Shortness of Breath										X
Other										
Product	Ripped Fuel Andro Heat Max Alert	ephedrine	Mini-Thin	Source Naturals Diet-Phen	ephedrine HCl	Mini-Thin	Ripped fuel Ultimate Orange	E-Z Trim	Advocare	Mini-Thin Meta Form Diet Max
Starting Amount/day 1 tab = 25 mg.	50 mg.	1 tab	2 tabs	3 caps (mg?)	225 mg.	4 tabs	400 mg.	2 caps (mg?)	1 cap (mg?)	3 caps (mg?)
Current/Ending Amount/day 1 tab = 25 mg.	100 mg.	1 tab	0	3 caps (mg?)	150 mg.	6 tabs	?	0	2-3 caps (mg?)	10 caps (mg?)
Length of Use	8 years	2 years	5 years	1 year	3 years	?	3 years	1 day	months	?

Age	2/22/70 29	3/27/79 20	12/1/53 46	10/20/70 28	3/21/77 22	7/27/64 34	2/21/71 28	3/13/72 27	7/13/78 20	6/5/69 29
Gender	Female	Male	Female	Male	Female	Male	Female	Male	Male	Female
Marital Status	Divorced	Single	Married	Divorced	Single	Married	Married	Single	Single	Married
Location	California	Ohio	Kansas	Tennessee	New Hamp.	Alabama	Pennsylvania	Australia	Ohio	California
Addicted/Dependent			X	X		X				X
Rapid Heart Beat				X	X		X	X	X	X
Blackouts				X	X					
Difficult Urination				X		X				
Irregular Heart Beat				X	X					X
Seizures										
Body Aches	X		X	X	X					X
Nervousness/Tremors	X		X	X	X	X	X	X		X
Paranoia				X						
Chest Pain				X	X					
Insomnia				X	X					X
Hallucinations			X	X						
Headaches	X				X		X			X
Stomach Upset				X	X	X				X
Shortness of Breath				X	X					
Other				Dehydration, rash, constipation, irritability, impotence						Hypothyroid, infertility
Product	Metaboslim	Diet Fuel Ripped Fuel	Superior Power	White Cross Mini-Thin	Black Cross	Max Alert	ma huang	ephedrine HCL	EPH 833 Dynetadrine Thermadrine	Omnitrim Metabolife
Starting Amount/day 1 tab = 25 mg.	36 mg.	2 RF (mg?) + 3 DF (mg?)	3 caps (mg?)	5 tabs	3 tabs	2 tabs	2 caps (mg?)	3 tabs	2-3 caps (mg?)	3 caps (mg?)
Current/Ending Amount/day 1 tab = 25 mg.	36 mg.	8 RF (mg?) + 12 DF (mg?)	1-2 caps (mg?)	30-40 tabs	12 tabs	18 tabs	2 caps (mg?)	3 tabs	2-3 caps (mg?)	0
Length of Use	months	months	months	8 years	5 years	11 years	1 year	1 year	2 years	3 years

DATA	191	192	193	194	195	196	197	198	199	200
Age	4/28/73 28	11/17/70 28	11/10/70 28	7/24/75 23	8/74 25	9/21/82 16	5/31/64 34	2/13/66 33	2/27/69 30	9/9/79 19
Gender	Female	Male	Male	Female	Female	Male	Female	Female	Male	Male
Marital Status	Married	Single	Single	Married	Single	Single	Married	Married	Married	Single
Location		Georgia	Missouri	Oregon		Texas	California	Indiana	Louisiana	Florida
Addicted/Dependent		X	X	X	X		X	X	X	X
Rapid Heart Beat	X	X	X	X	X	X	X	X	X	X
Blackouts	X		X					X		
Difficult Urination	X	X	X		X	X	X		X	
Irregular Heart Beat	X		X				X		X	X
Seizures										
Body Aches		X	X			X	X		X	
Nervousness/Tremors	X	X	X	X	X	X	X	X	X	X
Paranoia			X			X	X		X	
Chest Pain			X				X		X	
Insomnia	X		X	X	X	X	X		X	X
Hallucinations			X				X		X	
Headaches	X	X	X	X	X	X	X		X	
Stomach Upset	X		X	X	X	X	X		X	
Shortness of Breath			X	X			X		X	
Other			Skin problems	Dehydration Cancre sores			Depression Moody General Malaise			
Product	Ephedrine Plus	Max Brand	White Cross Mini-Thin Sudafed Bronkaid	Mini-Thin	Bronksid	Two Way	ma huang ephedra	AM-300	Mini-Thin Max Alert	Mini-Thin Ephedrine + Two Way White Cross
Starting Amount/day 1 tab = 25 mg.	6 tabs	1-2 tabs	?	6 tabs	40 mg.	3 tabs	40-120 mg.	12-24 mg.	3 tabs	1-3 tabs
Current/Ending Amount/day 1 tab = 25 mg.	10 tabs	18-24 tabs	500-1500 mg 3 or 4 times a day	3 tabs	"several boxes"	5 tabs	20 mg.	6-12 mg.	120 tabs	10-30 tabs
Length of Use	1 year	4 years	?	?	?	?	2 years	1 year	5 years	3 years

DATA	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Age	3/13/44 55	6/8/55 43	8/10/62 36	11/7/82 16	6/10/78 20	3/14/62 37	8/10/81 17	7/29/80 18	5/18/78 20	2/24/77 22
Gender	Female	Female	Female	Male	Male	Male	Female	Female	Male	Female
Marital Status	Married	Married	Married	Single	Single	Single	Single	Single	Single	Single
Location	Iowa	Utah	Oklahoma	Missouri	South Dakota	Oklahoma		N. Carolina	Louisiana	Kentucky
Addicted/Dependent			X	X	X					
Rapid Heart Beat		X	X	X	X	X	X	X	X	X
Blackouts				X						
Difficult Urination				X	X				X	
Irregular Heart Beat		X		X	X					
Seizures										
Body Aches	X			X	X			X		
Nervousness/Tremors		X		X	X		X	X		X
Paranoia					X	X				
Chest Pain					X			X	X	
Insomnia				X	X		X		X	
Hallucinations				X						
Headaches			X	X				X		
Stomach Upset	X			X	X			X		X
Shortness of Breath				X	X				X	
Other		Hysteria			Impotence			Anorexic & wants to lose more!		Anxiety attacks
Product	Hydroxycut	Max Alert	Fast Track Advocare	Blast Caps Super Tab Mini-Thin	aphedrine Fad 7	Ripped Fuel	Stacker 2	Diet Fuel	Mini-Thin	Diet Fuel
Starting Amount/day 1 tab = 25 mg.	334 mg.	1 tab	2 FT (mg?) + 2 A (mg?)	12 tabs	not daily	6 caps (mg?)	3 caps (mg?)	3 caps (mg?)	10 tabs	1-2 caps (mg?)
Current/Ending Amount/day 1 tab = 25 mg.	334 mg.	1 tab	?	16 tabs	8 tabs	6 caps (mg?)	1 cap (mg?)	9 caps (mg?)	6 tabs	1 cap (mg?)
Length of Use	months	?	3 years	3 years	2 years	1 year	weeks	months	months	9 days only

DATA	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Age	7/20/78 20	1/7/79 20	3/19/67 32	1/14/66 33	6/59 39	4/16/69 30	11/30/70 28	2/27/76 23	2/24/73 26	[illegible]/78 20
Gender	Male	Male	Female	Female	Male	Female	Female	Female	Female	Male
Marital Status	Single	Single	Married	Married	Married	Married	Single	Single	Divorced	Single
Location	England	Georgia	Illinois			Texas	Wisconsin	California	Wisconsin	
Addicted/Dependent				X	X				X	X
Rapid Heart Beat	X	X	X	X				X	X	X
Blackouts										
Difficult Urination										
Irregular Heart Beat				X				X	X	
Seizures										
Body Aches									X	
Nervousness/Tremors		X	X	X	X			X	X	X
Paranoia		X							X	X
Chest Pain			X	X					X	
Insomnia	X	X			X			X	X	X
Hallucinations		X								
Headaches	X								X	X
Stomach Upset				X				X		X
Shortness of Breath		X						X	X	
Other		3 wks. in hospital for psychotic episode			depression mood swings			edgy, shaking, vomiting		
Product	ephedrine	ma huang ephedra	ma huang ephedra	Ephedrine Plus Max Alert	Two Way	ephedra	Ephedrine Plus	energy boost drink and yohimbe	Ephedrine Plus Mini-Thin Ephedrine HCL Max Alert	Mini-Thin Two Way
Starting Amount/day 1 tab = 25 mg.	1 cap (mg?)	1-2 caps (mg?)	6 caps (mg?)	4 tabs	6 tabs	?	?		5 tabs	2 tabs
Current/Ending Amount/day 1 tab = 25 mg.	1 cap (mg?)	6-8 caps (mg?)	0	30 tabs	4 tabs	?	30 tabs		50 tabs	30 tabs
Length of Use	1 year	5 years	1 year	5 years	?	2 years	5 years	one time only	?	3 years

DATA	221	222	223	224	225	226	227	228	229	230
Age	5/10/??	7/8/63 35	10/13/61 37	12/15/75 23	4/18/70 29	8/24/52 46	8/17/70 28			
Gender	Female	Female	Male	Female	Female	Female	Male			
Marital Status	Single	Single	Married	Married	Single	Married	Single			
Location		Illinois	Texas	Wisconsin	Texas	California				
Addicted/Dependent	X			X	X		X			
Rapid Heart Beat	X			X	X					
Blackouts				X						
Difficult Urination							X			
Irregular Heart Beat		X		X	X					
Seizures										
Body Aches	X	X								
Nervousness/Tremors	X			X	X	X				
Paranoia					X					
Chest Pain				X	X					
Insomnia	X	X		X	X					
Hallucinations										
Headaches		X			X					
Stomach Upset	X				X					
Shortness of Breath					X					
Other		"Screwed me up"								
Product	Mini-Trim	Herbalife	Metabolite	Efedrin	ma huang	ma huang	ephedrine HCL			
Starting Amount/day 1 tab = 25 mg.	2 tabs	3 caps (mg?)	8 caps (mg?)	4 tabs	6 caps (mg?)	75 mg.	20 mg.			
Current/Existing Amount/day 1 tab = 25 mg.	5-6 tabs	0	8 caps (mg?)	16 tabs	"varies"	75 mg.	40 mg.			
Length of Use	?	?	2 years	8 years	4 years	1 year	4 years			

Mr. BURTON. Mr. Woosley.

Dr. WOOSLEY. Good afternoon, Chairman Burton and members of the committee. I am actually a physician; I am a pharmacologist and physician.

Mr. BURTON. Excuse me, Dr. Woosley.

Dr. WOOSLEY. No problem. It gave me a chance to emphasize the fact that I am a physician.

I have to say I am moved and even shaken to follow the previous two witnesses. I reviewed the FDA reports of their children's deaths, and I have to tell you it was difficult then, and it is more difficult now. I read those cases of—as they described, young children unknowingly taking poisons.

I have helped the FDA analyze these cases, and that is one of the reasons that I am here today. I have helped them analyze these and many other cases, and I would like to tell you that there is nothing wrong with that process. It can be made better, but it doesn't make mistakes.

Since 1977, I have conducted clinical research and basic research on the mechanisms of the adverse effects of drugs in humans. In over 250 scientific publications, I have examined the toxic effects of prescription and nonprescription drugs, mainly on the heart.

My research has identified the mechanisms responsible for the potentially lethal cardiotoxic effects of several drugs, including Seldane, a widely prescribed antihistamine recently removed from the market.

I mention my background because it is this experience upon which I base my conclusions and the recommendations to you today. You have asked this panel to address a very serious question, and I don't appreciate the levity that some have introduced; it really seems inappropriate.

This question has major consequences for the health and welfare of many citizens in our Nation. You have heard testimony from others that there are major weaknesses in the FDA's voluntary reporting system; and I also have criticized it in the past, but usually for what it has not done, not for what it has done. Some have tried to cast doubt on the data that comes from the FDA's surveillance system. Please don't allow them to confuse you on this issue.

In 1994, I was asked by the attorney general of the State of Texas and the Center for Food Safety and Applied Nutrition at the FDA to review 88, and later another 147, cases. These were cases of suspected toxic reactions of ephedrine-containing products. I have enclosed a copy of my initial report to the FDA for the record.

As you will see, in 1994 I concluded that there were reports of chest pain, heart attack, stroke, seizures, cardiac arrest, sudden death, two that we have heard today, some of these people in the prime of their lives. I concluded that these reactions are perfectly consistent with what one would expect to see from excessive dosage or extreme sensitivity to ephedrine.

In August 1996, I served as a member of the FDA Food Advisory Committee to review all of the scientific evidence that had been accumulated by the FDA. The FDA has done due diligence. They have had a process—perhaps it hasn't been made known to everyone, but they have seriously investigated this issue. There was full agreement by this committee that the 800 cases submitted to the

FDA were absolute proof of the harm associated with dietary supplements containing ephedra.

I and others have constructively proposed improvements to the FDA's current voluntary reporting system because it has inadequate staff. It often requires months to years before identifying an adverse event associated with a drug or a devise. The system is plagued by underreporting, incomplete reports, and inadequate staff for analysis of those reports. However, no credible argument has ever been made that the system makes errors in detection. It is a blunt instrument, but an essential one, that is capable of identifying frequent, serious problems, especially when they are closely associated with exposure to a product, as in this case.

In 4 years, over 800 reports of adverse events associated with over 100 different ephedrine-containing products were received at the FDA, 100 different, not just a few rebel products, 100 different products. The FDA has estimated that less than 1 percent of serious adverse drug reactions ever get reported. Therefore, the actual number of reactions to ephedra is far greater than the number that they have on record.

I have absolutely no doubt of the validity of the harm detected by the FDA scientists. In the past, the adverse drug reactions detected by the systems have been routinely confirmed by regulatory scientists in other countries that have used a wide range of different methodologies. An important part of the FDA system is the confirmatory process applied in the analysis of these, often less than adequate, reports. For example, because we know that ephedrine increases the blood pressure and heart rate in animals and in people, the profile of adverse events that you would predict to occur would be arrhythmias, stroke, cardiac arrest, and sudden death. These are exactly the kind of reactions I reviewed in those reports.

Additional confirmation is obtained by comparing the patterns of reactions to those seen with drugs that have similar pharmacologic action, such as amphetamine and methamphetamine. These have been the exact same kind of events reported with ephedrine.

Additional evidence for the reliability of the association is seen in the fact that 26 percent of the 800 reports included documentation that the adverse events subsided when the product was withdrawn. Further, in 4 percent of the cases, the exact same symptoms recurred when they reinstituted the therapy or the drug was again administered.

In summary, the FDA's spontaneous reporting system accurately detected and confirmed the harm that results from compounds containing ephedra. The public must be protected from the proven harm of these products.

Because of the biologic variability in the way people respond to these products and the fact that many people don't know that they have conditions which predispose them to the products harmful effects, such as coronary artery disease, it is impossible to identify a safe dose of these products.

I sincerely request that you give your strong support to the FDA's efforts and affirm their authority to take even stronger action and remove every one of these products from the marketplace.

When my 7-year-old son grows up and goes to Florida on spring break, don't let these products kill him.

Mr. BURTON. Thank you, Dr. Woosley.

[The prepared statement of Dr. Woosley follows:]

Testimony for the Hearing Record

Raymond L. Woosley, MD, PhD
Francis Cabell Brown Professor of Experimental Therapeutics
Professor and Chairman
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"How accurate is the FDA's monitoring of supplements like Ephedra?"

Committee on Government Reform

Congress of the United States

House of Representatives

May 27, 1999

1:00 PM

Introduction:

Good afternoon, Chairman Burton and Members of the Committee. I am Raymond L. Woosley, MD, PhD, Professor and Chairman of the Department of Pharmacology at Georgetown University Medical Center. I have submitted my Curriculum Vitae for the record but as a preface to my statement, I wish to mention that in 1967 I obtained a PhD degree in pharmacology, a field of study of the actions of drugs. I also obtained an MD degree and in 1977 I completed specialty training at Vanderbilt University in internal medicine and subspecialty training in clinical pharmacology, the study of the actions of drugs in humans. I was on the faculty of Vanderbilt for 12 years and for the last 11 years, I have been in my current position at Georgetown. Since 1977, I have conducted clinical and basic research on the mechanisms of adverse effects of drugs. In my over two hundred publications, I have primarily examined the toxic effects of drugs on the heart. I was co-director of the Cardiac Arrhythmia Suppression Trial, an NIH sponsored study that identified the deadly and unsuspected effects of antiarrhythmic drugs. I later identified the mechanism responsible for the potentially lethal cardiotoxic effects of Seldane, an antihistamine recently removed from the market. I am now conducting research to determine the molecular basis for the two fold greater risk of this toxicity for women treated with Seldane and forty other commonly prescribed drugs. I mention my background because it is this experience upon which I base my conclusions and recommendations to you today. You have asked this panel to address a very serious question that has major consequences for the health and welfare of the citizens of our Nation. I thank you for the opportunity to give you my perspective.

You will hear testimony that there are major weaknesses in the FDA's voluntary reporting system and some people may try to cast doubt on the FDA's interpretation of the data from this system. They may even quote my previous statements and publications in which I have criticized the FDA's voluntary reporting system for drugs. However, please do not allow them to confuse you with statistical or pseudo-scientific analyses of the data.

Ephedra, ephedrine, ma Huang

I will only briefly review the pharmacology of ephedra, ephedrine and ma Huang. The Chinese herb, ma Huang, was used for centuries as a stimulant, asthma medication and sinus decongestant. Ephedra is an extract of the herb containing the major active chemical, ephedrine. Ephedrine has been used in the past to treat asthma and sinus congestion but when newer and safer drugs became available, such as pseudoephedrine, phenylpropanolamine, salbutamol, etc, modern physicians stopped using ephedra and only rarely recommend the use of ephedrine. Newer, safer, more reliable, more consistent products are now available and there is little if any medical need for ephedrine products. Like all chemicals that are structurally related to adrenaline, amphetamine and methamphetamine, ephedrine can cause "a high" due to its stimulating effects in the brain. This leads to habituation, personality changes, including paranoid behavior, aggressive and destructive behavior. Doses that cause stimulation in the brain also are associated with increased blood pressure, rapid heart rate, abnormal heart rhythms, seizures, stroke, heart attacks and deaths.

In 1994, I was asked by the Attorney General of the State of Texas and the Center for Food Safety and Applied Nutrition of the Food and Drug Administration to review 88 cases of

suspected toxic reactions to ephedrine-containing products. I have enclosed a copy of my report to the Food and Drug Administration. As you can see, there were reports of chest pain, heart attack, stroke, seizures, cardiac arrest and sudden death (two people ages 36 and 43). I concluded that these reactions are perfectly consistent with what one would expect to see with excessive dosage or extreme sensitivity to ephedrine. I also concluded that the epedrine-containing products in those reports constitute a real and serious health risk to anyone who may take them.

In August of 1996, I served as a member of a Food Advisory Committee to review all of the scientific evidence that had been accumulated by the FDA. There was almost unanimous agreement on the Committee that the cases reported to the FDA were proof of the potential harm associated with the dietary supplements containing ephedrine. I and about half of the committee members concluded that there was no safe dose of ephedrine that could be recommended for the products when taken as dietary supplements. The other half of the committee felt that some low dose could be identified but no one was confident that such a dose would have any beneficial effects.

The FDA Voluntary Adverse Event Reporting System

I and others have criticized the current voluntary reporting system because it has inadequate staff and often requires months to years before identifying an adverse event associated with a drug or device. The system is plagued by under-reporting, incomplete reports and inadequate staff for analysis of the reports. However, no credible argument has ever been made that the system makes errors in detection. It is a blunt instrument but one that is capable of eventually identifying frequent serious problems especially when they are closely associated in time with exposure to a product. In four years, over 800 reports of adverse events associated with over 100 different ephedrine-containing products were received by the FDA. For any serious reaction to a drug, the FDA has estimated that as little as 1% of serious reports are ever even submitted to the FDA. Therefore, the actual number of reactions to ephedrine is sure to be far greater than the number received.

I have no doubt of the validity of the association detected by the FDA. In the past, the adverse drug reactions detected by the FDA's voluntary reporting system have been routinely confirmed by other countries that have used a wide range of different methodologies. An important part of the FDA's system is the confirmatory process applied in the analysis of the reports. For example, because we know that ephedrine increases blood pressure and heart rate in animals and in people, the profile of adverse events to these products should include arrhythmias, strokes, cardiac arrest, sudden death. These are exactly the reactions seen in the reports. Additional confirmation is obtained by comparing the types of reports to those seen with drugs that have a similar pharmacologic action. Chemical analogs such as amphetamine and methamphetamine have the same type of adverse events reported. Additional evidence for the reliability of the association is seen in the fact that 26 percent of the reports included documentation that the adverse event subsided when the product was discontinued. Furthermore, in 4% of the 800 cases, the exact same symptoms of the adverse event recurred when the product was taken again by the patient.

Another area of serious concern is the fact that there may be untested and unforseen dangerous interactions between these products and prescription drugs. Recent surveys indicate that 38% of patients refuse to tell their physician that they are taking a botanical "dietary supplement." When ephedrine-containing products are taken with beta blockers, the ability of these potentialy life-saving drugs to prevent heart attacks can be canceled. These drugs have never been formally tested for interaction with any of the many prescription drugs on the market today.

Summary and Conclusions

The FDA's spontaneous reporting system accurately detected and confirmed the harm that one would expect to result from compounds containing ephedrine. In the past when the drug was being used for medically proven indications, in consistent dosages and under the supervision of physicians and other healthcare providers, the low risk of these events was acceptable. Now that there are safer alternatives and the drug is being used for non-medical "recreational" purposes, the risk/benefit ratio is unacceptable and the public must be protected from the proven harm of these products. Because of the biologic variability in the way people respond to ephedrine-containing products, and the fact that many people do not know they have conditions that predispose to serious side effects (unknown coronary artery disease, hyperthyroidism, hypertension, etc), it is impossible to identify a safe dose of these products. I sincerely request that you yield strong support to the FDA's efforts and encourage them to take even stronger action to remove all of these products from the marketplace.

Mr. BURTON. I have a granddaughter and a grandson, and I share your concern about their exposure to things that could harm them.

Let me ask you a question. You reviewed the reports on the two young people who died. By any chance in those reports did you notice how much ephedra they had taken?

Dr. WOOSLEY. We tried to estimate that based on their labelled content, but in the FDA hearings it became very clear that you can't. FDA scientists collected those products that were being marketed then and measured their ephedra content. The content of ephedra and ephedrine-like alkaloids varied from 1 milligram to 100 milligrams, even though they were labeled to contain on average about 12 milligrams. We have no way of knowing how much these two young people took. The other aspect of it is it really doesn't matter how much it was, any amount could have been lethal.

Mr. BURTON. It is of concern. I take Sudafed and my wife takes a product that she uses for her asthma.

Dr. WOOSLEY. But that is not ephedrine. That is Sudafed. That is a much weaker compound. It is a totally different drug.

Mr. BURTON. All right. We will get back to that. That may be a layman's understanding.

Dr. WOOSLEY. This is a potent, toxic drug.

Mr. BURTON. What I would like to understand, when your son was in Florida and he took this, as I understand it, that particular product was advertised as giving people some kind of a feeling of euphoria?

Ms. SCHLENDORF. Yes, a feeling of euphoria or an energy boost or 100 other things.

Mr. BURTON. Right.

Ms. SCHLENDORF. It was also stressed that it was perfectly safe and harmless. Pete took at least four pills, could have taken as many as eight. His friends said they thought he took four. We were trying to account for all of them, so there could have been a couple more than four, but they didn't think that they were taking anything dangerous.

And what came out in our investigation of the pills and of the company, the company didn't know how much ephedra was in the product; and one box could have varied greatly to the next. We don't know how much he took.

Mr. BURTON. And I don't like to get into too much of the detail because it is not comfortable for everybody, but the autopsy that was performed, I presume, did it indicate in any way how much of this product or this substance was in his system?

Dr. WOOSLEY. I don't remember in this specific case, but I recall in several of the cases there was analytical data indicating the quantity in the body.

The problem with all of that is, it doesn't really matter how much is in the body or even in the pills. There are people who are exquisitely sensitive. He may have been such a person.

In the hearings, I argued long and hard but failed to win the argument that there is no safe dose of ephedrine as a dietary supplement because there is no way you can give it to a large number

of people without hurting an exquisitely sensitive person, for example someone who didn't know that they have high blood pressure.

Mr. BURTON. There are some products that I might buy over the counter which are perfectly legal and very safe for healthy people to take that might cause hives or severe problems for other people in my family, so that may not be unique to ephedrine.

Let me ask Dr. Farber about this. Doctor, Dr. Woosley has indicated that there is no safe amount of ephedra that can be taken, and you seem to have some expertise in this area. Can I have your opinion on that.

Mr. FARBER. Yes. I can't agree with Dr. Woosley. It is almost contrary to what every pharmacologist or toxicologist knows. Over 400 years ago, the father of modern toxicology said that the poisoning is in the dose and so forth.

And for a pharmacologist to say that there is no level of a material that is safe is mind boggling to me. There is a safe level of ephedra alkaloids; and the products of the responsible companies in this industry which do have proper labeling presents a product to millions of individuals that can be taken safely every day, and, in fact, billions of servings have been taken by people over the years.

This would, indeed, make this product safer than peanuts and shellfish and chocolate and strawberries and aspirin and wine; and I could go on and on and on in regards to products that we all use with the concept that we are using it safely, that, in fact, has produced a higher incidence of reactions in the public than these products.

Mr. BURTON. Do you have a comment, Dr. Mowrey?

Dr. MOWREY. In the ephedrine hearings that took place in 1995 and 1996, I believe those were the years that Dr. Woosley was a part of, questions came up about what is the history of toxicology with ephedrine hydrochloride prescribed at a dose of 150 milligrams per day, which is over twice as much as what we are saying is—is established in the research on ephedrine or ma huang currently in use.

Somebody said there isn't any. I can't remember who that individual was, but the point was that with all of the millions and millions of doses of that ephedrine hydrochloride that have been administered, such as in Primatine, which does contain ephedrine, there is virtually a total lack of this kind of toxicology that we are discussing here today.

And so the idea of a disconnect was suggested. There is some kind of a difference between the alkaloids present in ma huang and those in ephedrine; and it was an open question at that time.

Since then there has been research published to demonstrate the pharmacokinetics of ephedrine in ma huang is virtually identical to the pharmacokinetics of ephedrine hydrochloride. I think we have settled that issue at least temporarily in view of maybe we need more research along those lines, but I think that question has been addressed and the initial response is that they are fairly identical in their reactions in the body.

Mr. FARBER. Mr. Burton, could I make another comment?

Mr. BURTON. Sure. Go ahead.

Mr. FARBER. Dr. Mowrey brings up an important point in regards to Primatine and some of the products that are offered to millions of Americans in over-the-counter preparations. Primatine contains ephedrine, and the labeling allows for a dose level as high as 150 milligrams a day.

With the dietary supplements that we are talking about right now put out by responsible companies, the labeling suggests that there be no more than an exposure of 100 milligrams of ephedrine alkaloids, not necessarily ephedrine, but ephedra alkaloids; and some of those alkaloids are weaker, in fact, than ephedrine.

But it is interesting to note that people out there are taking Primatine at 150 milligrams a day—and at one time several years ago it was as high as 300—taking 150 milligrams a day and having ubiquitous contact with caffeine in coffee, in tea, in chocolate, in cola beverages; and there are no significant number of AERs being reported or in the files of the Food & Drug Administration. Doesn't that raise some questions? Thank you.

Mr. BURTON. Dr. Soller, has there ever been any analysis as to what is a safe amount of ephedrine and what is an excessive amount of ephedrine? Obviously Ms. Schlendorf's and Ms. Michal's sons took amounts that were excessive and did end up in their demise.

How do we know what is a safe amount, and what do we tell the American people?

Mr. SOLLER. Thank you. It is always difficult to try and be objective when you are—and deal with the science when you are dealing with tragic stories; and of course, we very much reach out to the parents, knowing that we have children as well.

And so with that and attempting now to step back and think objectively and what we know about the science, there has been a review of ephedrine through the OTC review that began in 1972 and subsequent reviews as well; and as a bronchodilator, ephedrine is used both as an inhalation form and an oral tablet.

Inhalation it will be about 5.5 milligrams per inhalation and then wait about 5 minutes and take another dose. And for the tablet, a total of a 25 milligram dose taken on a 4-hourly basis.

Now, information that has been sent in to FDA in reviewing this particular issue looked at the drug abuse warning network and found that ephedrine is fairly low on the list in terms of potential for abuse, that is, reports of an abuse situation to an emergency room setting.

And that is not particularly unusual in the OTC field because it is at the issue of a low potential for abuse, not absence of abuse. But what was backed up in that particular data-set for ephedrine was a 15-year cohort of AERs reported to companies finding that in a period where about a billion OTC tablets were sold, there were 171 adverse experiences and 3 of those were serious reports. There were no deaths.

So there appears to be a different situation on that OTC side than on this other side, and I would just like to make one or two more comments that kind of rounds out a view in terms of what I have heard here.

That is that the main issue here is for CFSAN to focus in on the safety of dietary supplements, and I would agree with Dr. Woosley

that we have basically a system in effect at FDA which can be refined.

And even on the drug side, Jane Henney knows that there needs to be refinement by CDER, and we would suggest that same systems approach be put through all centers, including CFSAN, and that we do not get into the kinds of situations where we are arguing the administration of AERs but we are looking at the science and carefully documenting. That is very important to do.

The other aspect is that GMPs are very important to the industry, and we have commented to FDA and urged that GMPs be adopted into regulation that would be somewhat different than food GMPs, not quite as high as drug GMPs for appropriate technical reasons we need not get into.

But that is very important because it would raise the issue of identity and concentration within the particular dietary supplement and would very much help, as you would get reports from the field that would talk about unknown amounts.

And if a company doesn't know what is in their particular product from an identity standpoint, it is our belief that raising the level of awareness on GMPs, allowing FDA to have that standard of inspection, would help the field and some of the occurrences that we have heard about today.

Mr. BURTON. Thank you. Ms. Schakowsky.

Ms. SCHAKOWSKY. Thank you, Mr. Chairman. Since we are talking today about accurate reporting, I just wanted to elaborate a bit. We are talking about 500 voluntarily made adverse event reports on dietary supplements. That was Mr. Levitt's comment.

But I asked him later privately, and he said that is a tiny number of adverse events, that is how many were reported under this voluntary system, that is all there were. When I said 1 percent, he seemed to indicate that was more like it.

So I think it would be a mistake for us to conclude that there are not any adverse events larger than 500. But I wanted to also ask Dr. Farber in the interest of accurate reporting, Dr. Farber, do you have or have you had any kind of a financial relationship with a dietary supplement manufacturer of an ephedra product?

Mr. FARBER. I have been retained by the law firm of Hyman, Phelps & McNamara that represents several diverse companies in the dietary supplement industry.

Ms. SCHAKOWSKY. And you said that AERs are useless. That was your testimony.

Mr. FARBER. No, I really didn't.

Ms. SCHAKOWSKY. No, I wrote that down. You said AERs are useless.

Mr. FARBER. In this particular instance, they are close to worthless. I could show you some further information in regards my analysis on these AERs. I have personally spent, and my associate, over 700 hours examining every one of the AERs in the public docket. If you are interested, I can show you the analysis.

Ms. SCHAKOWSKY. What I am interested in is the AERs that were filed by Ms. Schlendorf regarding her son Peter. Is that worthless?

Mr. FARBER. No. No. I didn't say that. I said that when you look at the whole situation, there is very little that is—that you are able

to interpret. Now, I have looked at the Schlendorf file, and I have looked at the autopsy report. I feel very sad for Mrs. Schlendorf in regards to this situation, but regrettably this young man took an illicit street drug, masquerading, perhaps, as a dietary supplement, and regrettably lost his life.

I don't condone the marketing of this product. Neither do the people that I have been working with or the industry that I have been trying to help. They are appalled that these products have been allowed to remain in the marketplace.

The Food & Drug Administration, indeed, had the powers under DSHEA to remove these products before Peter bought the product. They did not take the action that they were permitted by DSHEA to take against these things.

Ms. SCHAKOWSKY. I thought that you testified that it is safer than peanuts.

Mr. FARBER. I said when the products of the responsible industry companies are taken according to the labeled instruction on the product that they are safe and they are effective. That is not to say—I am not saying that abuse potential doesn't exist with ephedra. It does.

But I know—and it has been recently established—I think you are familiar with the Physicians' Desk Reference. I think almost every American has looked at this book to check on side effects of drugs. There is a new PDR on herbal remedies. That PDR says that ephedra is safe at levels up to 300 milligrams a day.

Now, the responsible members of this industry are recommending that their labeling state not to take any more than 100 milligrams a day.

Ms. SCHAKOWSKY. Thank you, Doctor. I would like to let Dr. Woosley respond to a number of things that were said here today. Go ahead, Dr. Woosley.

Dr. WOOSLEY. Thank you for that opportunity. I think it is very important to point out that the PDR and the PDR for herbals is simply a compilation of materials submitted by manufacturers. It has absolutely no other special credibility.

I would also defend myself as a pharmacologist in my statement that ephedrine has no safe effective dose as a dietary supplement. You can give 25 milligrams, 50 milligrams, 75 milligrams of ephedrine to everybody in this room and no one will ever feel anything more than a rapid heart rate and a headache and maybe trivial side effects.

But if you give it to millions the way that it is happening today, you get hundreds, or tens at least, of people dying like the ones that we heard about today, even at the low dose that is currently being recommended with no, absolutely no, proven benefit other than a high.

Do we want to recommend products be out there that can kill when there is no proven benefit?

Ms. SCHAKOWSKY. Could I go on for a minute. Just to underscore that, I am looking at some of the marketing of this product on the Internet.

Psychedelic Shrooms. Take a psychedelic magic carpet ride with the greatest pill on earth. Contains ephedra, sinac, whatever that is.

Then we have got each capsule contains 800 milligrams of ma huang extract; dosage orally, one to two capsules on an empty stomach 30 to 40 minutes before activity. Do not exceed recommended dosage.

We have got Midnight Ecstacy, Herbal Coke, Turbo Charge, all being advertised right now on the Internet.

Dr. Tim Johnson said on the tape this morning that he felt that ephedra should be acknowledged as a drug and therefore should be regulated as a drug, and I would like to hear the doctors' comments on whether or not they agree with that.

Mr. FARBER. Clearly the products that you have discussed—and I can go on and name many, many more like Brain Wash, Cloud 9, Ultimate Xphoria, Love Potion 69 and so on and so forth—they have all been taken out of the market at least by action of the Food & Drug Administration.

These products are winding up on the Internet, and the Food & Drug Administration has to work out some game plan to take action against these products. They are illicit street drugs; they are not dietary supplements.

Ms. SCHAKOWSKY. Should ephedra be regulated, as Dr. Tim Johnson said, as a drug?

Mr. FARBER. No, I don't believe so. If these dietary supplements are used according to the label—and the labeling on these products are almost identical to the labeling on Primatine—they can be used safely and effectively by the public without having to turn them into prescription items.

Ms. SCHAKOWSKY. And what is a safe dose?

Mr. FARBER. A safe dose would be 25 milligrams a day four times a day, not exceeding more than a 100 milligrams per day of ephedra alkaloids. The literature indicates that 25 milligrams per kilo four times a day is a safe dose even in the presence of caffeine. And you can go back into the literature.

Ephedrine had been derived from ephedra 75 years ago by K.K. Chen who became the scientific director of the Eli Lilly Laboratories. It has been extensively studied. We do know its pharmacology and what its side effects and toxicity is.

It is not a substitute for methamphetamine. For somebody to say it has the potency of methamphetamine and it has the capability of producing highs like amphetamine is wrong.

The DEA has acknowledged that it is not a substitute methamphetamine, and the United Nations has indicated that this material is not a drug or a substance that has any particular high level of drug abuse potential, and that has been as late as March of this year.

In fact, there is a letter to Congressman Farr from the State Department declaring that ephedra is considered by the United Nations to be not a significant drug of abuse.

Ms. SCHAKOWSKY. Mr. Chairman, I wanted to ask that the accompanying materials to Ms. Michal's statement also be put into the record; and she seems really anxious, so say something.

Mr. BURTON. Without objection. Ms. Michal.

Ms. MICHAL. Thank you very much.

As far as the addiction and abuse and the effect of ephedrine mimicking amphetamine, it is an amphetamine analog. It is molec-

ularly similar to amphetamine. It has been proven in studies by Dr. Paul Wellman at the head of the department of psychology at Texas A&M University that it affects dopamine in the brain exactly the same way cocaine and amphetamine do.

I mentioned that I was getting these reports from people over the Internet. I have just two comments that I would like to share with you as far as ephedra not mimicking amphetamine or giving them the same feeling.

I have a 40-year-old female from California reported that she was addicted to speed. She is a recovering drug addict. She took a product called Power Trim, two pills as per the label, took it once and she said, I knew right away it is the same stuff that I took when I was addicted to methamphetamine.

I have another one that basically said the same kind of thing. She was a former drug addict addicted to meth—a female, 24 from Oklahoma, and she took two pills, took it once of Advantage A.M. 300, and it was the same reaction: this is the same stuff that I was addicted to before, and I can't take it again.

Ephedrine is an amphetamine analog. I have a 48 percent addiction report rate, dosage run-ups to incredible levels.

Ms. SCHAKOWSKY. Mr. Levitt, is it true that those are illegal on the Internet? Are those drugs that I was referring to that are being marketed on the Internet, are they, in fact, illegal according to the FDA, which is what Dr. Farber said that those are illegal?

Mr. BURTON. We might ask him to return to the table after we conclude with this panel.

Ms. SCHAKOWSKY. I'm sorry.

Mr. BURTON. That is fine.

Let me just end up by asking one or two more questions. I want to make a comment. Dr. Woosley, you said that the food supplement industry did that PDR, but as I understand it from my staff, that PDR is based on the German government's commission and monograph. Is that correct?

Dr. WOOSLEY. There is something called the German Commission Monographs that is a translation of the monographs on herbal preparations.

Mr. BURTON. Is that the one to which you were referring?

Dr. WOOSLEY. No, that is a different document. The PDR for dietary supplements is a separate book and it is—Medical Economics markets these products.

Mr. BURTON. As I understand it, the industry took their PDR from the German government's?

Dr. WOOSLEY. They may have taken parts of it, but it is a form of advertising. It is not a scientifically rigorous document.

Mr. FARBER. Mr. Chairman, if I could make a comment.

Mr. BURTON. Dr. Farber.

Mr. FARBER. I have extensively used the German Commission E monograph, not AufDeutsch, but the English translation, and clearly ephedrine is recognized as a useful herb and recognized to be safe at dose levels considerably higher than 100 milligrams per day. The West German government has set up this commission, and it is heavily dependent upon the opinions found in these monographs.

Mr. BURTON. Let me ask Dr. Mowrey one more question. Dr. Dickinson, because we have not asked you a whole bunch of questions does not mean that we don't value your contribution.

Dr. Mowrey, can you give us any information about ephedra and how it works on fat metabolism?

Dr. MOWREY. This is a fairly new application for ma huang. It has its historical roots in the science of thermogenesis, and in particular in the discovery that brown adipose tissue in human beings is truly capable of significant thermogenesis in terms of its ability to help the body in its efforts to control weight.

Ephedrine turns out to be the only safe and effective molecule that we know of today to really activate this process in the body via sympathetic mediation. The process is under the control of the sympathetic nervous system, and we stimulate that with ephedrine.

There is plenty of research to support the contention that it is a safe and effective treatment for obesity in human beings. Like I say, it is the most popular treatment throughout Europe. Ephedrine/caffeine combinations there account for 80 percent of the weight loss market, and considerable research has been generated by Arn Astrup and a group in Denmark to demonstrate the efficacy and safety of this particular combination.

Granted, there are mild adverse events that occur, as we have been mentioning here, but serious adverse events are not seen in that research. That research, the subjects of course are screened so they don't have cardiovascular complications coming into the research. Labels are designed to help screen out people from taking the product that might be susceptible to that kind of an accident.

In the United States the Harvard group led by Patty Dailey with Lawrence Lanceburg on the team established the safety and efficacy of long-term treatment of human beings with an ephedrine, caffeine, and aspirin combination. That was published in the International Journal of Obesity in 1993.

Since the publication of that document, there has been a dramatic increase in interest in this particular mechanism for weight control. I think that it represents right now perhaps the boldest and the best program that we have for controlling weight because it seems to address the underlying physiology of the problem.

In fact, most of the genetic research going on right now with leptin and other genetic mutations all seem to have as a common pathway metabolism in adipose tissue, in particular brown adipose tissue.

So it's a very strong thrust for the medical profession right now to be involved in doing this, and it is, I suppose, what has led the dietary supplement industry into producing products that contain those substances.

Mr. BURTON. OK. Well, let me just say to all of you how much I appreciate your time and your patience.

Once again, our condolences to both of you. We will certainly take into consideration everything that you two have said, as well as Dr. Woosley. We sure have heard a diverse group of opinions here. So thank you very much.

We would like to have Mr. Levitt return to the table just for a couple of seconds. Mr. Levitt, thank you for being patient and sticking with us for a little bit here.

I think what I would do is I will initially yield to Ms. Schakowsky, and then I just have a couple of questions for you, Mr. Levitt, esquire.

Ms. SCHAKOWSKY. Thank you so much, Mr. Chairman. I really appreciate this opportunity.

Let me ask you directly then what I had mentioned before. The 500 voluntarily made adverse events reports represent, in your view, what percent or how much of the total adverse events that occur with dietary supplements?

Mr. LEVITT. Well, we believe with all regulated products that the reports that get submitted is a tiny percentage of what is really out there, because people don't necessarily either make the connection themselves or even if they make the connection think that either—either don't know where to report it to or don't know how to or aren't sure what is going to become of it.

So we estimate, even in the pharmaceutical area, that reporting is in the neighborhood of 1 percent of what really is out there.

Ms. SCHAKOWSKY. So would it be accurate then to conclude, because there are so few reported cases then, that there are, therefore, so few problems out there?

Mr. LEVITT. Well, I think it is hard to say that. What I think it is important to say is that the point of the adverse event reporting system, and I appreciate the chance to emphasize this, is to signal a potential problem. And even with under reporting, which is accepted in all of these systems, the chances are high that somebody is going to report it and then FDA has a chance to see it and check other data bases, other existing information, check the literature and, see, yes, do we think this signal is right.

So there is definitely under reporting, as there are with all of those. What we hope is reported is, if you will, an illustrative example and we can pick from even under reported important signals that can identify safety problems.

Ms. SCHAKOWSKY. Thank you so much for that.

I also wanted to clarify whether or not these drugs that contain ephedra, that are advertised over the Internet, are they—is that illegal to purchase them and to offer them for sale?

Mr. LEVITT. OK. The rule on that is that if these products are—contain what we would consider a drug claim, that makes them subject to the drug rules. Now what you have there is we have had to go back and say are there—by the kind of title that they give the product, by the kind of statements, if they are really essentially marketing it as an alternative to street drugs, that we will consider that a drug and in this case, since we know they don't have premarket approval as an approved drug, then they would be illegal.

But the fact that they are illegal doesn't mean that it is easy to chase down. Things market over the Internet. FDA can try to do something. It is very simple for somebody to change their website, alter their name a little bit, and it is very much a difficult process to chase these people down.

Ms. SCHAKOWSKY. So it is a subjective conclusion on what they are claiming to be? I mean, energetic sensations, waves of sensual

pleasure, gentle tingling sensations, states of nirvana, is this illegal?

Mr. LEVITT. The actual analysis of those is done by a different part of the FDA so I am not expert in the specifics, but that is the general point. The general point is how—if in the jargon that is used, if what they are really saying is that this is an alternative street drug, it is used for recreational purposes, it is not identified for weight loss or for something that is a normal mainstream use, then that would make it a drug claim and not lawfully marketable.

Ms. SCHAKOWSKY. Thank you.

Mr. BURTON. Thank you, Ms. Schakowsky.

Mrs. Schlendorf's and Ms. Michal's children lost their lives because of the over use or over—excessive consumption of these pills.

They have been taken off the market by the FDA, have they not?

Mr. LEVITT. You mean those particular ones?

Mr. BURTON. Yes.

Mr. LEVITT. My staff are telling me yes.

Mr. BURTON. What I would like to know, and followup to what Ms. Schakowsky just asked, is were the advertisements fairly consistent with what she just read for these other things that are on the Internet?

Mr. LEVITT. I—you don't know? Are they fairly consistent with what——

Mrs. SCHLENDORF. Yes, they are, and I also know that the exact product Ultimate Xphoria that my son took, it was recommended to take four and he only took four to maybe eight. That particular product is no longer manufactured. The company is still in business and they are manufacturing other similar things.

Mr. BURTON. OK.

Mrs. SCHLENDORF. There are lots of other things on the Internet very similar that any 10-year-old can buy. Those have not been taken off the market.

Mr. BURTON. OK. Thank you.

I would like to ask, Mr. Levitt, can't the Federal Trade Commission work with you to get these products that are being advertised on the Internet, that are using similar advertising techniques, can't they followup and try to run these people down?

I know that there are some "Internet police" now that are out there trying to get unscrupulous people off the Internet. It seems to me that the same thing could be done for these products that are endangering young people with excessive amounts of ephedrine.

Mr. LEVITT. Well, there are mechanisms that we are using.

Mr. BURTON. OK.

Mr. LEVITT. And shall continue to use for those.

But may I just say I think it is a mistake, and at least a number of the testimony in the previous panel suggested that the evidence and the adverse events that we have found are not limited to those that are viewed as "high abuse levels." The questions that were basically asked were five.

No. 1, are there consistent patterns of signs and symptoms associated with the use of these different ephedra alkaloid containing products? And the answer to that was yes.

Two was, are the patterns consistent with the available scientific evidence and known physiologic and pharmacologic effects of

ephedrine alkaloids? The answer was yes. The answer I am giving here was the answer from our Foods Advisory Committee.

Three, does exposure occur temporarily before the onset of the observed scientific symptoms, meaning did they take the product first? The answer was yes.

Is there other evidence of causality, meaning dechallenge, rechallenge? Dr. Woosley referred to that also, and the answer was yes.

And then the question was, considering the totality of the available information, is there a biologically plausible explanation for the adverse events? And the committee concluded, I believe unanimously, that the answer was so.

Mr. BURTON. Was there any indication from that about the amount?

Mr. LEVITT. There was a number of views expressed about the amount. Some expressed Dr. Woosley's view that it would not be possible to establish a safe amount. Others on the committee suggested that FDA try and establish a safe level. That's what FDA tried to do in the proposed rule and so forth.

If I may, just one other point that is related to this. Appended to my written testimony is a chart that I would just like to put up briefly because it was—so much of this was addressed by the previous panel, because I think, again, a point that is often misunderstood. There are a lot of adverse events, some of them more serious than others, some less serious, obviously, than others, and we have talked about that. But what FDA did, and what is important to understand about the system in general, is that the point of those reports is not to give you a definitive answer. The point of those reports is to signal, is there a potential problem here? If they do, what else can we look at?

And the chart here shows, you start really at the bottom. What is in the literature that we know about it? Are there any controlled clinical trials? In this case, there were some trials dealing with weight loss. What do we know about the OTC drug experience? What do the experts say?

We take all of that together and say, is this supporting a global finding that there is a public health problem with these products? And they unanimously said, yes.

And so I was appreciative of some of the prior testimony about the FDA process. Before, we talked mostly about the process in general, but this is a case where the system did identify a real public health issue.

People are struggling on exactly what is the right remedy. You referenced that. Is there a safe dose or not a safe dose? How many different products are out there? Is it some products and not other products?

There is a lot of complexities to the issue, but I think that should not take away from the underlying finding. And the Timothy Johnson segments, I think, underscored that, that there is something going on here that we need to try and remedy and do the right thing about that.

We are trying to do that, but I think, as you have also seen, it is a challenging labyrinth to get all the way through.

Mr. BURTON. Obviously there are some strong differences of opinion.

Mr. LEVITT. Right.

Mr. BURTON. The thing on the Internet, though, and we are going to review all of this information that has been submitted by everybody, the thing on the Internet is really important and you are going to put these disclaimers on there, you say, to try to make sure that people don't——

Mr. LEVITT. Yes. You mean the webpage, yes.

Mr. BURTON. On the webpage, right.

I would like to ask Dr. Yetley one last question. Is she still here?

This is on a different subject, but since we have you here I would like to ask you about it. We have received hundreds of letters from the public regarding the Codex Committee on Nutrition and Food for Special Dietary Use. There are a lot of consumers that are concerned that through an international governing body, upper limits will be set on the dosage of their vitamins.

Can you give me an outline of what the controversy is on that real quickly?

Mr. LEVITT. Could I just say, thank you for asking that question because again there is a lot of misinformation out there about that. I am sure Dr. Yetley can explain.

Mr. BURTON. Thank you for prefacing her comment with that. I appreciate that.

Ms. YETLEY. Thank you. The Codex Committee is an international standard setting committee. It is part of the WTO agreements, or at least it feeds into those.

There is a proposal on the table that was forwarded by the German government, which is proposing to set standards for vitamin and mineral supplements that would include both minimum and maximum levels.

First of all, let me make it very clear that even if the Codex Committee were to adopt these standards, it would not affect the products in the United States. The products under DSHEA would still have jurisdiction here. So it would not affect availability of these products in the United States.

This issue has come up before the Codex Committee on Nutrition and Foods for Special Dietary Use for the last two meetings. The U.S. position has been to oppose this particular standard because it is not consistent with our laws. However, the rest of the delegates have, as a majority, wanted to move forward.

We are now in the process of offering to work with other governments to write a background paper that would lay out the pros and cons of the various perspectives of different governments and different delegations. So it will give us a chance to lay forth our philosophies and concerns as well as other governments'.

Mr. BURTON. We would like to, if it would be possible, Doctor, to have you meet with our staff for a full briefing.

Ms. YETLEY. I would be glad to.

Mr. BURTON. We would really appreciate it.

Mr. LEVITT. I think that it is just indicative of the fact that these products are regulated differently in different countries, and when you get into different international fora, everybody tries to move it.

Mr. BURTON. Sure. We would like to have a briefing just so we can understand that better.

Mr. LEVITT. Sure.

Mr. BURTON. Mr. Levitt, thank you very much. Doctor, thank you very much.

We I want to thank all of our witnesses. It has been a long day. We really appreciate it, and we hope this has shed some light on this whole problem. The meeting stands adjourned.

[Whereupon, at 4:45 p.m., the committee was adjourned.]

[Additional information submitted for the hearing record follows:]

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6/9/99
Committee on Government Reform
The Honorable Dan Burton, Chairman
2157 Rayburn House Office Building
Washington, DC 20515-6143

Honorable Congressman Burton and committee members;

The American Association of Oriental Medicine is the oldest and largest professional organization of acupuncture and Oriental Medicine providers in the United States, and as such represents the profession in cases such as are before your committee now.

The FDA has a direct impact on our ability to procure and provide herbal supplementation as a part of our practice, supplementation that our profession has historically provided its patients for thousands of years. Yes, Oriental Medicine providers have a multi-millenium legacy of the use of these herbs and a historically accurate written background that makes present day research look shabby in its scope and verified effect on millions if not billions of people over that millennia. This clinical information was passed down through the ages in medical texts, and while the cultural bigotry of today's medical "science" can't fit it into pigeonholes satisfactory to their ability to grasp how it is done, it is a complete science of its own and requires study of its own. This is the quandary.

Unless the science behind the medicine is used, the context and efficacy are lost. The Oriental Medicine practitioners who use herbs in this country on a daily basis use this legacy effectively and safely, and have been tested by either a state or national certification agency to meet standards developed by the profession and implemented by many state's acupuncture and Oriental Medicine boards in those states. This is as it should be.

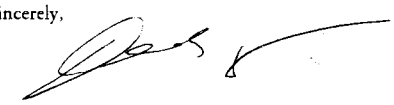
The AAOM cannot speak for manufacturers who use our herbs in ways developed outside of our field. We can only work within our field to ascertain the quality of our practitioners and to work to make sure that those who do use the Oriental Medicine construct for diagnosis and the use of herbal supplements meet standards developed within the field for efficacy and safety. We have started the process of developing an adverse event reporting body within our organization to facilitate this type of data gathering. Since our budgetary constraints restrict, or at least slow the development of this process down, we would be pleased to have the FDA work with us to develop it to its fullest potential. We do not have any fear of the FDA with regards to gathering of data, just in their use and interpretation of it, since they have historically been antagonistic to anything their blinders wouldn't allow them to see, and also that they do not use herbs, or anything for that matter, that they cannot understand within their medical paradigm. Chinese herbs work best when used in the context of the Oriental Medicine medical construct, and are not amenable to the same types of studies that are used for drugs due to the individualized nature of the diagnosis and treatment in Oriental Medicine.

Our profession is on the healthcare professions vanguard of the public's fascination with herbal medicine, and our focus is to provide safe, effective, competent, and ethical care using all the modalities that Oriental Medicine can provide. To do this, our organization has pushed the envelope of educational advancement for our profession, its accreditation and certifications agencies, and our members. We are willing and able to work with the FDA and any other agencies to enable them to provide competent and useful regulatory oversight in any aspect of Oriental Medicine, but have never been approached to do so. We can only hope this changes as these agencies are made more aware of their inflexibility and the results of that inflexibility on the health of the public. We realize that no agency wants to learn a new language or to allow autonomy in something they don't understand, and that the inflexibility we see is the result of human nature and the politics of medicine, and we look forward to having the Committee on Government Reform clarify, for the public, the inclusionary views we express.

In summary, we look forward to working with the FDA and any other agencies on the development of an adverse event reporting body that our profession can work with, perhaps similar to the one used in Australia. We do feel that, if herbs are removed from common availability, that Oriental Medicine practitioners who have shown by examination and credentialing criteria to have the highest available standards in the United States in the use of herbal medicine should continue to have access to any herbs or materials presently in our materia medica's as published in both Chinese and English. And lastly, we wish to reiterate that agencies of the United States government must have professionals who are Oriental Medicine professionals participating in the decision-making processes of its agencies such as the NIH, the FDA, the VA, the HCFA, HHS, and other agencies that have an impact on our practice. The problem is and has been the continuing lack of educated professionals in these agencies who have any true awareness of what it is that Oriental Medicine professionals do or even what their educational criteria are. To assume that a medical professional from another medical paradigm (allopathy) can grasp the breadth of a entire field of medicine (oriental medicine) in a short period of time and understand it well enough to make regulatory and other decisions on any aspect of the other field borders merely shows the lack of any meaningful education in the subject.

The AAOM sincerely hopes that we will someday be working closely with regulatory agencies to provide the best possible oversight to health care in the public's best interest. We thank you for your interest.

Sincerely,



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June 10, 1999

BY FAX AND FEDERAL EXPRESS

Honorable Dan Burton (R-IN)
Chair
Committee on Government Reform
U.S. House of Representatives
2157 Rayburn House Office Building
Washington, D.C. 20515-6143

Attn: Elizabeth Clay

Re: Hearing on FDA Monitoring of Nutritional Supplements

Dear Congressman Burton:

We are general counsel to the National Nutritional Foods Association (NNFA), the nation's largest trade association of suppliers and retailers of dietary supplements.

Enclosed for inclusion in the record of the above-referenced hearing, which was held on May 27, 1999, is the written testimony of Michael Q. Ford, NNFA's Executive Director.

Respectfully yours,

Charles J. Raubicheck

CJR:dmp
Enclosure

cc (w/encl.): Michael Q. Ford
Edward J. Long

U.S. House of Representatives
Committee on Government Reform
Hon. Dan Burton (R-Ind.), Chair

Hearing on FDAMonitoring of Nutritional Supplements

May 27, 1999

WRITTEN TESTIMONY OF
MICHAEL Q. FORD
Executive Director
National Nutritional Foods Association

I am Michael Q. Ford, Executive Director of the National Nutritional Foods Association. NNFA, founded in 1936, is the largest trade association of suppliers and retailers of dietary supplements and health foods in the country. I appreciate the opportunity to address you today regarding the FDA's monitoring of dietary supplements, such as ephedra, to protect the public against serious adverse events.

First, it must be emphasized that FDA has ample statutory authority, under Section 403(f) of the Federal Food, Drug, and Cosmetic Act, to take appropriate regulatory action against unsafe dietary supplements. This provision of Federal law authorizes FDA to institute seizures, criminal prosecution or injunction court enforcement proceedings if a dietary supplement presents a significant or unreasonable risk of illness or injury under the conditions of use recommended or suggested in the product's labeling. FDA also has authority under Section 306 of the FD&C Act to send warning letters to manufacturers, and under Section 705 of the Act to issue public warnings to consumers, about unsafe dietary supplements.

Unfortunately, FDA has not always made use of these statutory tools entrusted to it by Congress. Notably, rather than take court enforcement action against certain supplements containing the dietary ingredient ephedra (an herbal source of ephedrine) at inordinately high levels (some with labeling claims offering the products as alternatives to illicit street drugs), the agency instead instituted a rulemaking proceeding against all ephedra-containing supplements, irrespective of ephedra content or labeling claims. This proposal would, if finalized, effectively wipe out the entire product category of supplements containing ephedra by imposing unduly restrictive ephedra content levels. FDA's primary basis for the proposed content limits consist of 13 adverse event reports (AERs) received by the agency, in which ephedra-containing dietary supplements were allegedly involved.

Significantly, no definitive causal relationship between ephedra and the adverse event reported was established in these instances, due to lack of critical information such as reliable serum concentration data and laboratory analyses showing the amount of ephedrine per capsule ingested. FDA has not released the documentation within its possession underlying these AERs, despite a Freedom of Information Act request for them that was filed many months ago.

While NNFA does not oppose a responsible use of AERs as a basis for determining that a supplement presents a significant or unreasonable risk of illness or injury, FDA's reliance on these deficient reports clearly appears to have been inappropriate. As noted in NNFA's comments on FDA's ephedra rulemaking proposal (copy attached), the agency's expert

advisory group that considered the same AERs found no definitve association between serious adverse events and ephedra.

It is self-evident that, if FDA intends to rely on an AER system as a main basis for making safety decisions posed by particular dietary supplements, the agency must undertake an adequate investigation of the AERs upon which it grounds these decisions. In such an investigation, FDA should obtain personal interviews, relevant documentation and reliable analyses concerning each incident, and should rely upon an AER only if such evidence is available and demonstrates to a reasonable degree of scientific certainty that the dietary ingredient in the supplement product directly caused or significantly contributed to the injury reported. If necessary, FDA should obtain independent expert opinions to make or support its causation or contribution finding.

Recently, representatives of NNFA and three other dietary supplement trade associations met with Joseph Levitt, Director of FDA's Center for Food Safety, and urged the agency: (a) to terminate the ephedra rulemaking proceeding, and (b) to adopt a compliance guideline under which FDA would take court enforcement action against ephedra-containing dietary supplements that exceed a rational serving size level (up to 25 mg. four times daily), or fail to include appropriate label warnings. This serving size level and warnings have been adopted in the States of Ohio and Texas.

Such a guideline, coupled with a meaningful AER program that assesses causation on the basis of reliable and necessary data, should provide a sound basis for FDA to carry out its public health responsibilities under Section 403(f) of the FD&C Act for ephedra-containing dietary supplements. The same degree of meaningful AER documentation and assessment would also allow FDA to fulfill such responsibilities for other dietary supplements that may be implicated in future adverse event reports.

Thank you.

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December 2, 1997

Dockets Management Branch (HFA-305)
Food and Drug Administration
Room 1-23
12420 Parklawn Drive
Rockville, MD 20857

Attn: Michael A. Friedman
Lead Deputy Commissioner of Food and Drugs

Re: Docket No. 95N-0304:
"Dietary Supplements
Containing Ephedrine Alkaloids"

Dear Commissioner Friedman:

We represent the National Nutritional Foods Association ("NNFA"), the largest trade association of manufacturers and distributors of dietary supplements in the United States. On behalf of NNFA, we submit the following comments on the above-entitled notice of proposed rulemaking published on June 4, 1997 (62 Fed. Reg. 30677-30724).

A. FDA Has Not Met Its Burden of Scientific Proof

This proceeding is based on a provision of the Dietary Supplement Health and Education Act of 1994 (DSHEA) that requires FDA to prove that a dietary ingredient "presents a significant or unreasonable risk of illness or injury." 21 U.S.C. §343(f)(1)(A). FDA has failed to meet this burden of proof. The same adverse event reports upon which the proposal is principally based were considered by the Special Working Group on Foods Products Containing Ephedrine Alkaloids of FDA's Food Advisory Committee. This Group found no definitive association between recommended dose levels of the dietary ingredient ephedra (the herbal source of

ephedrine contained in dietary supplements) and serious toxic effects in humans. This finding was undoubtedly based in part on the presentation made to the Group by Michael H. Davidson, M.D., Medical Director of the Chicago Center for Clinical Research. Dr. Davidson reviewed a substantial number of the adverse event reports and concluded: (i) "the vast majority of both serious and non-serious adverse reactions occurred with products that exceeded the dosage thresholds," and (ii) "there appear to be only rare possible associations of ephedra products with severe adverse events." A copy of Dr. Davidson's presentation to the Special Working Group is attached to these comments.

Nonetheless, FDA has ignored these expert conclusions and, based on no significant additional data beyond those reviewed by the Special Working Group and Dr. Davidson, has proposed unreasonable restrictions on ephedrine levels in dietary supplements containing ephedra as a dietary ingredient. FDA's position does not square with available scientific evidence or the advice of qualified experts, and clearly falls well short of the statutory standard prescribed by DSHEA.

B. The Ephedra Levels Found Safe by the State of Ohio Are Reasonable

The State of Ohio has by legislation established safe upper limits for ephedra in dietary supplements that are reasonable, given the available relevant scientific evidence. These are: (i) up to 25 mg. of ephedrine alkaloids derived from ephedra per dose, and (ii) a total daily intake of up to 100 mg. of ephedrine alkaloids derived from ephedra. The Ohio Legislature considered a substantial body of data and expert opinion in arriving at these levels.

NNFA believes that, if FDA decides to finalize ephedra limits for dietary supplements, it should adopt the above-stated Ohio levels. NNFA further believes that ephedra-containing dietary supplements should bear appropriate labeling recommending responsible use of these products. Such labeling should include a caution against taking the products at levels in excess of the limits noted above, and should provide information on a safe duration of use consistent with reliable scientific data.

C. Effective Date

NNFA urges FDA to adopt an effective date for any final ephedra rule that allows products already in the possession of wholesalers or retailers to be sold. Thus, if the final rule

continues to have a six (6)-month effective date, the effective date should apply to products labeled and shipped from manufacturing plants after that date.

NNFA thanks FDA for the opportunity to have commented on this proposal.

Respectfully submitted,

NATIONAL NUTRITIONAL FOODS ASSOCIATION

Joe Bassett, President
Michael Q. Ford, Executive Director

SIDLEY & AUSTIN
General Counsel

By _____
Charles J. Raubicheck
I. Scott Bass

Before The Food Advisory Committee

Food and Drug Administration

Meeting On

Dietary Supplements
Containing Ephadrine Alkaloids

Statement of

Michael H. Davidson, M.D., F.A.C.C.

August 27, 1996

Washington, DC

My name is Michael H. Davidson. I am a physician and a fellow of the American College of Cardiology. I am an assistant professor of Medicine at Rush Presbyterian-St. Luke's Medical Center. I am also the Medical Director of the Chicago Center for Clinical Research.

The Chicago Center for Clinical Research performs clinical trials for the food, drug and nutritional products industries. I have over ten years experience as a Principal Investigator of more that 200 clinical trials in evaluating adverse reactions occurring during the trials.

I have been retained by the National Nutritional Foods Association to review the Adverse Event Reports received by the FDA on Ephedra-containing products, and to determine if the recommendations of the Dietary Supplement Trade Associations are based on an appropriate medical rationale.

My interpretation of the adverse events was based on standard FDA criteria. An event was classified as serious if the event was one of the following:

1. Fatal
2. Life-threatening
3. Results in persistent or substantial disability
4. A congenital abnomaly
5. Results in or prolongs in patient hospitalization

The relationship to the Ephedra product was classified as:

1. Unrelated if another cause of adverse event was documented
2. Remote if another cause was far more likely to cause the event
3. Possible if the adverse event was associated with potential side effects of Ephedra products, but other causes of the adverse event were equally or more likely
4. Probable if the adverse event was likely associated with the Ephedra products

I have reviewed the Adverse Event Clinical Summaries found at Tab F in your materials. In addition, I have also reviewed the cases files underlying 187 of those adverse event summaries. Of these 187 case files, I categorized 82 of the events to be serious and 105 not to be serious.

Of the serious events, I found that twelve were not related to Ephedra. Twenty-seven were remotely related Twenty-two were possibly related and seven were probably related. I classified nine cases as unknown for lack of information.

Of the non-serious cases, I found that seven were not related to Ephedra and thirteen were classified as unknown for lack of information. Thirty-nine were possibly related and twenty-seven were probably related to Ephedra. Nineteen were remotely related and nine involved known or potential side effects.

I would like to focus on four areas of serious adverse events:

1. Death
2. Myocardial Infarction
3. Stroke
4. Seizures

There are 22 deaths reported out of approximately 600 adverse events. In my opinion, 12 deaths were either unrelated or remotely related to the Ephedra products. Six deaths were possibly associated with Ephedra. In two cases not enough information was provided to consider an assessment. Two deaths were related to the assumption of toxic doses of Ephedra. Of the six deaths possibly associated with Ephedra, three were due to sudden death, and cardiac abnormalities were present on autopsy in all three individuals. Two deaths were due to strokes. One death was due to a stroke that occurred in an obese male on multiple other supplements, and he had basilor artery atherosclerosis on autopsy. The other fatal stroke occurred in a 44 year old female, due to a left internal carotid artery occlusion. She had a very strong family history of strokes. The sixth individual whose death was from a seizure that was possibly attributed to Ephedra was also on phentaramine (Adipex®, an amphetamine-like drug for weight loss). All of the six possible deaths associated with Ephedra were on high dose products (Formula One, E'Ola Drops, etc.)

There were ten cases of non-fatal myocardial infarction reported. Of these 10 cases, four, in my judgment, were not related to Ephedra. In three reports, not enough information was provided to consider an assessment. In three reported cases, a possible association with Ephedra products exists. In all three reports, post myocardial infarction angiograms revealed normal coronary arteries. All three individuals were consuming high dose Ephedra in combination with caffeine. (Formula One in two cases and Metabolift Thermogenics in the other).

There were 17 reports of non-fatal strokes. Three cases were unrelated or remotely related to Ephedra products. In four additional cases, not enough information was

available. In the remaining ten cases, a possible association with Ephedra products exists. In four of the ten individuals, significant hypertension of hyperlipidemia was diagnosed prior to the stroke. One case involved a male with a dilated left ventricle as a potential source of emboli. The remaining five cases involve premenopausal women. At least two of the women were on oral contraceptives, one was noted to be a cigarette smoker and another was diagnosed with having a lupus inhibitor. In the three remaining cases, oral contraceptive use is unknown and one was a cigarette smoker and one of these women was on the product for over a year before she suffered an intracerebral hemorrhage. All of the stroke patients were on high dose Ephedra products.

There were 16 reports of seizure, of these cases, the majority of seizures occurred in individuals with a history of seizures, or were noted to have an abnormal EEG on follow-up.

In summary, with the exception of two cases of toxic exposure to ephedrine, there appear to be only rare possible associations of Ephedra products with severe adverse events. These rare possible associations are characterized by coronary or cerebral thrombosis and seizures.

The non-serious adverse events are characterized by increase in blood pressure, tachycardia, nervousness and dizziness. These symptoms are expected potential side effects of Ephedra products. These side effects appear to be dose related, occurring in greater frequency in the high dose Ephedra products.

Based on my medical review of the Ephedra adverse events, I have the following opinions.

1. The recommendations of the Ephedra working group are appropriate. The two main issues that appear to affect adverse reactions are the dose of Ephedra and quality assurance of the product. The proposal to lower the limits to 60 mg/day with 15 mg of Ephedra per dose provides a margin of safety based, or the fact that the vast majority of both serious and non-serious adverse reactions occurred with products that exceeded the dosage thresholds. Good manufacturing practice, and quality assurance will provide dosing consistency within products. Because dosing consistency is important, I would add to the recommendations that products that can be easily mis-dosed, such as drops not be permitted. This may explain the high incidence of adverse reactions in the E'Ola Amp II Pro Drops.

The Ephedra working group has also recommended very appropriate warnings and labeling instructions. I would also include on the label, cautionary warnings regarding oral contraceptives, cigarette smoking and history of cardiovascular or seizure disorders.

2. Clinical trials are necessary to better define the appropriate dose range. A dose titration toleration study should be conducted which evaluates Ephedra blood levels, side effects and clotting parameters.

3. In addition to the Ephedra Hot Line that industry is considering, I would also recommend an active surveillance program with approximately 1000 product consumers to better ascertain the frequency and severity of adverse reactions.

In conclusion, I would be happy to review with the Advisory members and FDA officials my rationale for deciding the relationship between the Ephedra products and the adverse events. These case reports of adverse events are often very complicated and if I can be of any assistance, I will be in Washington up until 3:00 pm today. Thank you and I am open for questions.

Michael H. Davidson, M.D. F.A.C.C.