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DIETARY SUPPLEMENT SAFETY ACT: HOW IS THE FOOD AND DRUG ADMINISTRATION DOING 10 YEARS LATER?

HEARING

BEFORE THE

OVERSIGHT OF GOVERNMENT MANAGEMENT, THE FEDERAL WORKFORCE, AND THE DISTRICT OF COLUMBIA SUBCOMMITTEE

OF THE

COMMITTEE ON GOVERNMENTAL AFFAIRS UNITED STATES SENATE

ONE HUNDRED EIGHTH CONGRESS

SECOND SESSION

JUNE 8, 2004

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DIETARY SUPPLEMENT SAFETY ACT: HOW IS THE FOOD AND DRUG ADMINISTRATION DOING 10 YEARS LATER?

TUESDAY, JUNE 8, 2004

U.S. SENATE,
OVERSIGHT OF GOVERNMENT MANAGEMENT, THE FEDERAL WORKFORCE, AND THE DISTRICT OF COLUMBIA SUBCOMMITTEE,
OF THE COMMITTEE ON GOVERNMENTAL AFFAIRS,
Washington, DC.

The Subcommittee met, pursuant to notice, at 2:36 p.m., in room SD–342 Dirksen Senate Office Building, Hon. George V. Voinovich, Chairman of the Subcommittee, presiding.

Present: Senators Voinovich and Durbin.

OPENING STATEMENT OF SENATOR VOINOVICH

Senator VOINOVICH. The Subcommittee will come to order.

Good afternoon, and thank you for coming. The Subcommittee is meeting this afternoon to discuss the Food and Drug Administration's implementation of the Dietary Supplemental Health Education Act of 1994, also referred to as DSHEA.

This hearing was requested by my friend and colleague, Senator Durbin. In the 5½ years that I have been Chairman or Ranking Member on this Subcommittee, Senator Durbin and I have had an excellent working relationship. When I was Chairman of the Subcommittee during the 106th Congress, we held two hearings on food safety at Senator Durbin's request, and during the last Congress, Senator Durbin held two hearings at my request on one of my top issues, human capital management, and today, I am happy to be hosting this hearing.

Prior to this hearing, I was not familiar with the subject matter of dietary supplements. After I started researching the issue, I began to understand why Senator Durbin wanted to hold a hearing. I take vitamins daily and would like to be guaranteed that they are labeled correctly and that they are safe. I also have additional concerns with people mixing dietary supplements and prescription drugs.

Millions of Americans buy and use dietary supplements on a daily basis and believe that the products that they are taking are safe and beneficial to their health. Now that we have reached the 10th anniversary of the act, it is appropriate to examine whether the FDA and the dietary supplement industry have adhered to the intent of this law so that Congress might consider ways in which it could be improved and also to educate American consumers on

the latest development in dietary supplement policies and practices.

Recognizing the need for the Federal Government to address the American consumer's growing interest in dietary products and public safety, Congress overwhelmingly passed DSHEA 10 years ago. And the purpose of the act was to provide the framework for ensuring that the Federal Government properly oversees the safety and efficacy of dietary supplements sold in the United States.

Essentially, this legislation requires that all ingredients and supplements sold in the United States must be previously approved by the FDA and listed on the bottle label and that distributors must follow guidelines to demonstrate the veracity of any claims that are made in regard to the particular product. Additionally, an important aspect of DSHEA is the establishment of good manufacturing practices, GMPs, which are standards that could help ensure the safety of dietary supplements.

In March 2003, the FDA published a proposed rule for dietary supplement GMPs, and the rule is currently under review. It is my understanding that the final rule on GMPs is expected by the end of the year. I applaud the Bush Administration and former FDA Commissioner McClellan for making this a priority. This is a positive step in the enforcement of DSHEA, and I hope these standards give American consumers of dietary supplements greater confidence in their safety.

With that said, I would like to know why it took the regulations so long to be established. Responsible members of this industry have actively sought appropriate science-based regulations to ensure that consumers are well-educated through factual labeling and that dietary supplements are manufactured in a consistent manner to guarantee their safety and efficacy.

Unfortunately, not all players in the market are responsible. It is these bad players that bring us here today. We need to ensure that they are held accountable and that Americans can depend on the existing regulatory agencies to protect and promote their wellbeing with regard to dietary supplements.

To aid in this dialogue, the Subcommittee will be hearing from the U.S. Food and Drug Administration, policy researchers, medical professionals, consumer advocacy groups, and dietary supplement industry leaders, regarding the impact of the law.

I now yield to our Ranking Member of the Subcommittee, my good friend, Senator Durbin, for an opening statement.

OPENING STATEMENT OF SENATOR DURBIN

Senator DURBIN. Thank you, Mr. Chairman. And this has been a very cooperative bipartisan relationship, and we each have our interests and priorities, and Senator Voinovich has allowed me to pursue this, and when I chaired this same Subcommittee, I offered the same opportunity to him.

And I think this is the kind of bipartisan cooperation people expect of us, and I am glad that we have been able to achieve it in this Subcommittee.

Mr. Chairman, 1994 was an important year in the history of the dietary supplement industry. After an overwhelming effort on Capitol Hill, the dietary supplement industry won the right to sell

their products to the American public without testing them in advance for safety or establishing their efficacy. The Dietary Supplement Health Education Act of 1994, also known as DSHEA, exempted the industry from informing the FDA when their products caused harm or injury to the people who were buying them.

The law that was passed in 1994 was opposed by all public health, medical, and professional nutrition groups, including the American Cancer Society, the American Dietetic Association and all of the major consumer groups in America, including the Consumer Federation of America.

Since then, business has been very good for the supplement industry. The industry has grown more than fourfold since 1994, from $4 billion to $18 billion in sales. According to the Centers for Disease Control and Prevention, more than 38 million Americans used dietary supplements in the past 12 months. The Internet has now grown to 143 million users, and there are literally thousands, hundreds of thousands of Websites on the Internet that sell dietary supplements.

But meanwhile, consumers have been endangered by the FDA's inability to act on particular supplements, 155 people died after taking dietary supplements containing the stimulant ephedra, and thousands more suffered injury. Yet it took years, literally years, for the FDA to ban this substance under this law, DSHEA. The FDA's action, though commendable, may have been a classic case of closing the barn door well after the horse had galloped away.

By July 2003, 6 months before FDA acted, Walgreens, CVS, Rite Aid, and virtually all other major drug stores and specialty nutrition stores in this country had already removed products containing ephedra from their shelves. Why? They believed that ephedra was too risky and exposed their stores to legal liability if they continued to sell dangerous ephedra products.

All the major American sports organizations and the International Olympic Committee had already banned ephedra before the FDA acted. Three of the most populous States, Illinois, New York, and California, had done the same, and the nation of Canada had banned the sale of ephedra. Ephedra products were banned for sale on military base exchanges around the world, because we had literally lost soldiers who had taken ephedra products and died.

Why did it take the FDA, the agency created by President Theodore Roosevelt to protect the American public from mysterious elixirs claiming to cure diseases, so long to finally pull the plug on ephedra? The answer? DSHEA. The law has to be changed to protect consumers. Millions of Americans take vitamins safely every day, including this Senator and the Chairman. Vitamins taken in recommended doses are safe.

It is the designer supplements that are worrisome. Supplement makers like to say their products are safe because they are natural. They have been used for years. But the truth is that many of today's supplements contain concentrated extracts mixed with a myriad of other ingredients that can be harmful. Take the supplement Joint Ease, which was marketed as a natural remedy for arthritis. While the active ingredient, aristolochic acid, has been used for centuries in Europe and China, the supplement product contained

the substance in concentrated form which was subsequently found to cause kidney failure and kidney cancer.

The product was eventually recalled, but only after cases in the United Kingdom, Belgium, and France highlighted its toxicity. Until we fundamentally change the law governing how supplements are regulated, agencies responsible for public health will constantly fall short of monitoring the marketing practices of this industry. I do not believe that every natural substance needs to be subject to premarket safety testing. But at the very least, DSHEA should be changed so that stimulants are tested before marketed. When a supplement raises blood pressure, increases metabolism and constricts blood vessels, it is only prudent that we test this product before it is marketed. Otherwise, American consumers are going to be the laboratory test rats.

Another change I would like to see made to DSHEA is making the adverse event reporting system mandatory for serious adverse events. I am not talking about someone getting dizzy from taking a supplement. I am talking about heart attacks, strokes, and death. It is absolutely necessary that we know when a product is seriously harming people. How can the FDA effectively protect the public if it does not know when the product is causing harm?

Adverse event reporting is not a cumbersome process compared to the premarket safety and efficacy review prescription and over-the-counter drugs go through. Fixing DSHEA and keeping dietary supplements safe are challenging tasks. It is no assignment for the politically timid, I can tell you, having been on this issue for a couple years. Regardless, our responsibility to protect the health of the American consumer is clear.

Thank you, Mr. Chairman.

Senator VOINOVICH. Thank you, Senator Durbin.

First, the Subcommittee has the pleasure of hearing testimony from Hon. Dr. Robert Brackett. Dr. Brackett is the Director of the Center for Food Safety and Applied Nutrition at the Food and Drug Administration. He will explain in greater detail the status of DSHEA's implementation.

On the second panel, we will hear from Dr. Alice Clark, the Vice Chancellor for Research and Sponsored Programs at the University of Mississippi and a member of the National Academy of Sciences' Task Force for Developing a Framework for Evaluating the Safety of Dietary Supplements. The Subcommittee will also hear testimony from Dr. Ron Davis, Member of the Board of Trustees of the American Medical Association to discuss the medical society's view of DSHEA. And we will also hear from two consumer groups: Charles Bell, who is the Program Director for Consumer Reports; and Bruce Silverglade is the Director of Legal Affairs at the Center for Science in the Public Interest. And to provide insight into how DSHEA has affected the dietary supplementary industry, the Subcommittee will hear from Tony Young, General Counsel for the American Herbal Products Association, which represents the herbal supplement industry and Dr. Annette Dickinson, President of the Council for Responsible Nutrition, who represents many suppliers, manufacturers, and marketers of dietary supplements in the United States.

I want to thank all of our witnesses for coming today. It is my sincere hope that this hearing will help point out the positive effects of the Dietary Supplement Health Education Act while at the same time providing suggestions from our witnesses that could further improve this law.

Once again, we look forward to hearing from today's witnesses. I would appreciate it if all of you could keep your statements to 5 minutes and please be aware that your statements will be made a part of the official record of this Subcommittee.

We have a custom here in this Subcommittee to swear in all witnesses. I would ask all of our witnesses today to stand and to raise your right hand, please.

[Witnesses sworn.]

Senator VOINOVICH. Let the record indicate they answered in the affirmative.

Dr. Brackett, will you come forward?

TESTIMONY OF HON. ROBERT BRACKETT, PH.D.,[1] DIRECTOR, CENTER FOR FOOD SAFETY AND APPLIED NUTRITION, U.S. FOOD AND DRUG ADMINISTRATION

Mr. BRACKETT. Good afternoon, Mr. Chairman and Senator Durbin.

I am Dr. Robert Brackett, Director of FDA Center for Food Safety and Applied Nutrition, and I am pleased today to testify before your Subcommittee on the Dietary Supplement Health and Education Act.

Many Americans take some type of dietary supplement, and in many cases, there is either strong or suggestive evidence that many of the vitamins and minerals and other sorts of naturally-occurring products that we take have important health benefits. The Dietary Supplement Health and Education Act of 1994, as you said, DSHEA, amended the Federal Food, Drug and Cosmetic Act to set up a distinct regulatory framework for these products in an attempt to strike the right balance between providing consumers access to dietary supplements that they may choose to help to maintain and improve their health and giving the Food and Drug Administration regulatory authorities to take action against supplements or supplement ingredients that present safety problems, either having false or misleading claims or otherwise adulterated or misbranded.

As with foods, there is no premarket FDA approval of safety for most dietary supplements. However, there is a 75-day premarket notification requirement for manufacturers of certain dietary supplements that contain so-called new dietary ingredients that were not marketed in the United States before October 15, 1994. In its new dietary ingredient notification to FDA, the manufacturer or distributor of the supplement must submit information that provides the basis on which it concludes that the dietary supplement containing the new dietary ingredient will reasonably be expected to be safe.

[1] The prepared statement of Mr. Brackett with attachments appears in the Appendix on page 43.

FDA regulates the safety of dietary supplements primarily through a postmarket evaluation of whether the product is adulterated under the provisions of the Food, Drug and Cosmetic Act. In developing a comprehensive postmarket safety evaluation of dietary supplement products, FDA collaborates with consumer and industry stakeholders as well as other Federal partners and academic centers.

An important tool that FDA uses for developing the so-called signal which might identify potential safety problems are adverse events reports. These reports are not mandatory and consist of voluntary reports from industry, health care providers and consumers.

Under DSHEA, FDA was given authority to promulgate regulations for dietary supplement current good manufacturing practices, CGMPs, and such regulations could help ensure product quality and consistency. FDA published a proposed rule on March 13, 2003; extended the comment period; convened two satellite downlink outreach meetings and attended three outreach meetings organized by the industry.

Publishing the final rule is a priority for FDA. The FDA uses three principles: direct health risk, indirect health risk, and economic harm to guide the development of its risk-based enforcement strategy. Products that are not themselves hazardous can still present an indirect health hazard in that consumers may delay or forego proven medical treatments or drug therapies. Examples include unproven products promoted for the treatment of cancer, diabetes, arthritis, heart disease, and high blood pressure.

This strategy provides a foundation for the agency's enforcement activities. However, we continually reevaluate our actions and emphasis in light of emerging issues or products to ensure that our activities achieve compliance.

Since October 2002, FDA has conducted 224 domestic inspections of dietary supplement manufacturers, issued more than 170 warning letters and cyberletters to marketers of dietary supplement products, seized products worth more than $9 million, supervised the voluntary destruction of more than $3 million worth of supplements with promoted and unsubstantiated dietary supplement claims or that were unapproved drugs and obtained permanent injunctions against five firms distributing misbranded or unapproved new drugs.

FDA enforcement has extended to our Nation's borders, where we have refused importation of more than 1,500 foreign shipments of potentially unsafe or misbranded dietary supplements offered for entry into the United States. The agency's enforcement actions send a clear message that FDA will not tolerate fraudulent practices that victimize or endanger consumers.

In April 2004, FDA sent a warning letter to 16 dietary supplement manufacturers making false and misleading claims for weight loss products promoted over the Internet. Many of these products claimed to block starch, carbohydrates, fats and calories while maintaining that consumers would lose weight without any changes in their lifestyle. On March 8, 2004, the producers and distributors of SEA-Silver signed a consent decree of permanent injunction in which they agreed to stop manufacturing and distributing violative products and agreed to destroy the seized products

at their expense and pay liquidated damages of $10,000 per day for any future violations of the consent decree.

Under a settlement with the Federal Trade Commission entered into on March 4, 2004, the SEA-Silver defendants and the individual distributors agreed to pay $4.5 million in consumer redress, and this consent decree followed a coordinated effort in June 2003 that resulted in the seizure of $5.3 million worth of products.

FDA will continue to use our available resources to fully implement DSHEA, and Mr. Chairman, I do thank you very much for this opportunity to testify today, and I would be very happy to take your questions.

Senator VOINOVICH. Thank you, Dr. Brackett.

Do you think that DSHEA gives the FDA the regulatory authority to supervise the dietary supplement industry?

Mr. BRACKETT. It does give us the supervisory authority to supervise the dietary supplement industry. But what is important is that we take what all of the parts of DSHEA and implement it fully in order to get the most use out of it.

Senator VOINOVICH. So it is your opinion that the law is adequate. Do you think that there are some improvements that could be made in the law that make it easier for you to get the job done?

Mr. BRACKETT. Well, the administration has no plans at this time to make any changes or suggest any changes to DSHEA. There are a number of options that we could use that would improve our effectiveness, including, especially, more research that could be done on some of the supplements themselves so that we could better define what they are and what they do.

Senator VOINOVICH. One issue that is of concern to this Subcommittee is the oversight of government management and restructuring, is the capacity of agencies to perform the jobs that they are asked to perform by Congress, in this particular case, DSHEA, the enforcement of it, I think in your testimony you said something about FDA does the job with "available resources."

Mr. BRACKETT. That is right.

Senator VOINOVICH. I know that FDA has numerous responsibilities other than enforcing DSHEA. Do you believe that you have the resources necessary to enforce this law?

Mr. BRACKETT. Well, we have the resources we need to do and enforce the top priorities. Part of our strategy is to look at all of the different issues that we have to deal with within DSHEA, prioritize them based on public health risks, as I had mentioned earlier and then to use our resources effectively towards those that have the biggest public health impact.

Senator VOINOVICH. What are the top priorities?

Mr. BRACKETT. The top priorities are looking at those ingredients that might cause some sort of injury or might otherwise cause human health effects. As I mentioned, we can also have indirect effects, where people are taking dietary supplements in lieu of taking medical treatments, but we are most interested in those ingredients that might actually have a direct public health impact; that is, make someone ill.

Senator VOINOVICH. How do you find out about those ingredients?

Mr. BRACKETT. Well, there are several different ways, one of which is the label. We look to see what is on the label and whether the ingredients listed on the label actually have characteristics, known pharmacological properties that——

Senator VOINOVICH. Do you have a regular policy of monitoring these supplements as they come onto the market? Or do you wait for these things to be brought to your attention by this adverse event reporting or from consumer groups that are out there monitoring new supplements?

Mr. BRACKETT. Well, all of the above. We have, as I mentioned, the 75-day notification in which a manufacturer of a new dietary ingredient would send in an application for their product being listed as a new dietary ingredient, where they must show cause that they believe that this product is safe, so that is one way.

Senator VOINOVICH. These are new ingredients. The law was passed 10 years ago and said that the ingredients prior to the passage of the law were grandfathered in.

Mr. BRACKETT. That is correct.

Senator VOINOVICH. So, if they come out with new ingredients that are different than what were grandfathered, they have an obligation to bring that to your attention?

Mr. BRACKETT. That is correct.

Senator VOINOVICH. If they do not do that, what is the penalty?

Mr. BRACKETT. They are subject to prosecution, because they are marketing this product that is not an approved new dietary ingredient. The other things that we do in addition to looking at——

Senator VOINOVICH. Pardon me; do you have many of those that do that?

Mr. BRACKETT. No, there are not many who do that. We have—probably more than half the applications that come in, we will object to, because they have not provided enough information, enough scientific information to justify that they are safe, and so, we are not aware of many that do that.

Some smaller items may, when we find out about them, we do take action for those. And as listed in my written testimony, there are a number of examples of those sorts of items that we have taken action on.

Senator VOINOVICH. About how many prosecutions have you had for people who failed to come in and comply with that part of the law?

Mr. BRACKETT. I am not sure of the exact numbers. I can find that out, and I would be happy to get back to you with the exact number.

INFORMATION PROVIDED FOR THE RECORD

Response: In March 2004, FDA sent 23 warning letters to companies asking them to cease distributing products sold as dietary supplements that contain androstendione (andro) and warning them that they could face enforcement actions if they do not take appropriate actions. The warning letters state that FDA assumes that the firm has a basis to conclude that androstenedione is a dietary ingredient. If androstenedione is a dietary ingredient, FDA believes that it is also a new dietary ingredient for which a premarket safety notification is required. Because any manufacturer or distributor who has received a warning letter has submitted no such notification, these products are adulterated and their marketing is prohibited under the Federal Food, Drug, and Cosmetic Act. The letters further state that FDA is, based on what it knows now, aware of no history of use or other information estab-

lishing that a dietary supplement containing androstenedione will reasonably be expected to be safe. In the absence of such information, these products would be adulterated even if the required premarket safety notification were submitted. The attached list has the names of the firms and the products in question. A sample warning letter is also attached.[1]

The Agency has never conducted a prosecution for violations of the notification requirements for new dietary ingredients.

Senator VOINOVICH. I would like that.

Mr. BRACKETT. OK.

Senator VOINOVICH. As you know, under DSHEA, FDA can regulate dietary supplement good manufacturing practices. I understand that FDA will issue a final rule on GMPs possibly by the end of the year. Can you tell me why it has taken so long for these GMPs to be issued and if you feel they will bring about needed changes in the oversight of the dietary supplementary industry?

Mr. BRACKETT. Well, I will answer your last part first, which is yes, absolutely; good manufacturing practices are essential to providing consistency and quality, and, as you mentioned earlier, to make sure that the consumers get what they think they are getting in an ingredient. There's a number of reasons why it has taken a long time. First, in 1994, when DSHEA was published, it took a little bit of time for FDA to, in making a current good manufacturing practice rule, finding out all of the background on the industry, what needed to be changed, what did not need to be changed.

And so, we spent a lot of time meeting with the industry in the intervening years. From that, we were able to propose the rule that you had mentioned earlier.

Senator VOINOVICH. When was that rule proposed again?

Mr. BRACKETT. In 1993.

Senator VOINOVICH. No, I am talking about the rule that——

Mr. BRACKETT. Oh, in March 2003 is the current proposed good manufacturing practice rule. Since that time, we have gotten much comment from the industry. We have met with them; have extended the comment period; we have gotten over 1,600 pages of comments that we very thoughtfully went through; hundreds of substantive comments that we will address in the final rule.

Senator VOINOVICH. I have run out of my time, but one question that I have got, and then, you can save it for the next one is that if the law was passed 10 years ago, it seems to me that is a long time to consider regulation.

Mr. BRACKETT. It is a long time, and that is why it is one of our top priorities within the Center for Foods.

Senator VOINOVICH. Thank you. Senator Durbin.

Senator DURBIN. Thank you, Mr. Chairman.

Dr. Brackett, I apologize. We are usually given biographies of the witnesses, and I do not have yours. Are you a medical doctor?

Mr. BRACKETT. No, I am not. I have a Ph.D. in food microbiology.

Senator DURBIN. I see.

Let me ask you a few questions, if I might. First, on the reporting of new ingredients, the 75-day reporting, was there a list published of pre-1994, pre-DSHEA ingredients so that FDA knows if there is a new ingredient that is being used?

[1] List of Manufacturers Receiving Androstenedione Warning Letters and Sample Warning Letter on Androstenedione, submitted by Mr. Brackett, appear in the Appendix on pages 66 and 68 respectively.

Mr. BRACKETT. To my knowledge, there was no specific list given on those ingredients.

Senator DURBIN. So how does that work?

Mr. BRACKETT. What FDA does, then, is goes back to look to see whether certain of the dietary supplements that we know were sold before that time were marketed, and of course, those we can rule out. Otherwise, it takes research to go back and find out whether there is any evidence that they were, and we also request from the industry to show whether or not they were marketed before that period.

Senator DURBIN. That seems like a very unusual approach, that FDA did not start off with a list of pre-1994 ingredients so the agency would have some knowledge as to whether an ingredient is new. Is it possible that some ingredients were benign in some combinations but dangerous in other combinations?

Mr. BRACKETT. Yes, that is true.

Senator DURBIN. So if you had an ingredient that perhaps was viewed as an old ingredient, had been used before 1994, now combined with another old ingredient, the combination itself could turn out to be dangerous; is that possible?

Mr. BRACKETT. It would be possible. I do not know of any specific examples, but that goes back to one of the important gaps that I think we have, which is do we actually characterize many of these ingredients to find out individually what they do and what their characteristics are? And then, when you also have the evidence-based reviews of these compounds, see if there is any evidence of cross-reaction with other compounds.

Senator DURBIN. So to protect American consumers, would not our government and your agency want to know a lot more about the ingredients used before 1994, particularly in what combinations they were used, and whether you are not only seeing new ingredients but new combinations of old ingredients? Are not all of those important questions if your mission is to protect the consumers?

Mr. BRACKETT. They are excellent questions, and that is information that we would like to have. That is true.

Senator DURBIN. And you do not have the right to establish that information under DSHEA, do you?

Mr. BRACKETT. Well, what we are doing is working with academic centers such as the University of Mississippi's National Center for Natural Product Research, with the National Institutes of Health, to try to get those answers.

Senator DURBIN. We are 10 years after the fact, and I am glad we are still working to try to get those answers as the industry has grown from $4 billion in sales to $18 billion in sales.

Now, let me speak about the GMPs, the manufacturing practices. How many years has the FDA been working on these regulations to establish good manufacturing practices in the dietary supplement industry?

Mr. BRACKETT. Well, I would say at some level, we have been working since DSHEA was passed. It has been the most active probably in the last 4 or 5 years.

Senator DURBIN. So for 10 years, the FDA has been trying to establish basic standards of manufacture and purity of the products themselves, not looking into specific questions about whether this

is a product that might be of some danger to an individual; is that correct?

Mr. BRACKETT. That is correct. Well, as I mentioned earlier in the testimony, one of the things we did early on was to go back and check what were manufacturers doing at that time? What were the industry norms within the industry themselves? Which sorts of operations would cause products to be either contaminated or whether they would be reduced, or perhaps the amount of an ingredient might not match what was on the label.

So we tried to learn as much about this industry as we could before we actually started writing.

Senator DURBIN. Are you familiar with a group called Consumer Lab, Dr. Cooperman and Dr. Obermeyer?

Mr. BRACKETT. I have heard the name, yes.

Senator DURBIN. I believe Dr. Obermeyer was a former employee of the Food and Drug Administration. In *Oprah Magazine,* they just published the fact that Theragran-M, which is a very common multivitamin, advanced formula, high potency multivitamin, multimineral contained 3.65 micrograms of lead, which exceeded the limit for supplements used by adults. Are you familiar with that?

Mr. BRACKETT. I have not read the article, and I have heard rumors about it but no personal knowledge of that issue.

Senator DURBIN. Now, going to Chairman Voinovich's question, Stuart Prenatal, a multivitamin, multimineral supplement, advertises that it has 4,000 IUs of Vitamin A. It turns out, after testing, it has 75 percent of the vitamin A that is claimed. Again, that is in the article which you are familiar with—or at least have heard of—but have not read. These are things which go to the question of good manufacturing practices, are they not?

Mr. BRACKETT. That is exactly what good manufacturing practices are for, and in addition to having too little vitamins, it is sometimes quite dangerous to have too much as well, so that is also covered.

Senator DURBIN. And we are still, after 10 years, trying to establish basic standards on good manufacturing practices.

Let me go to March 11, 2004, this year, where your agency announced a crackdown on companies selling androstenedione (andro), a steroid precursor. Acting FDA Commissioner Lester Crawford said we are using the DSHEA authority to supervise dietary supplements put on the market after the law was passed. For example, he said, we sent letters to 23 companies directing them to cease distributing dietary supplements containing andro.

Doctor, are you familiar with a company known as GNC?

Mr. BRACKETT. Yes, I am.

Senator DURBIN. Pretty widespread, large company with a lot of stores all over the United States.

This morning, I asked my staff to go over to the local GNC. They went over and purchased this product called Skuplt. It is a topical fat loss product containing androstenedione. It also contains yohimbine, a substance the FDA announced 11 years ago causes serious adverse effects, including renal failure, seizures and deaths.

Since the FDA has taken a specific action against this dietary supplement, and we still find it on the shelves of one of the most

prominent supplement retailers in the United States, what does it tell us about your enforcement actions?

Mr. BRACKETT. Well, with the letters that we sent out on androstenedione, I think all but five have withdrawn their products.

Senator DURBIN. Out of how many?

Mr. BRACKETT. Out of, I believe, 23.

Senator DURBIN. Twenty three.

Mr. BRACKETT. In this particular instance, did you say this was a topical?

Senator DURBIN. Yes.

Mr. BRACKETT. So this may not be covered under what we were looking at, which were oral dietary supplements.

Senator DURBIN. All right; now, let me ask you about the adverse event reporting. You said one of the things that you feel is your responsibility is to establish the risk of a dietary supplement product; is that correct?

Mr. BRACKETT. Yes.

Senator DURBIN. We ask the makers of prescription drugs—in fact, we do not ask; we require them to report adverse events so that the Food and Drug Administration will know if there is a warning sign. If someone gets seriously sick, hospitalized, dies from a prescription drug, the FDA is put on notice immediately. Did you not testify earlier that DSHEA makes this reporting by supplement manufacturers strictly voluntary?

Mr. BRACKETT. That is correct. It is voluntary.

Senator DURBIN. So how can you protect the American consumer from risk if you are not even receiving from these companies, the dietary supplement companies, notice that their products are hurting, injuring or even killing American consumers?

Mr. BRACKETT. Well, I think that the answer to that is that adverse event reporting, it is an important signal, but it is not the only thing that we use. Equally important are some of our knowledge of the pharmacology of some of the ingredients that might be in there with, even in the absence of an adverse event, whether we have used it against evidence-based reviews to see if there has been any reporting in the scientific literature and what the science actually points to on those ingredients as well as perhaps the chemical nature of the compounds themselves, whether they are similar to other sorts of ingredients that we know might cause public health problems.

Senator DURBIN. So it comes down to a basic question I will ask you: Either you are asking for too much information from the pharmaceutical companies on adverse event reporting, or you are not asking for enough information from the dietary supplement manufacturers, who have a voluntary reporting standard. Which is it?

Mr. BRACKETT. Well, we would welcome a lot more information from the dietary supplement manufacturers or, I think, information in general from wherever, whether it be physicians or the public as well, as again, as one of the parts of the signals that we use.

Senator DURBIN. Thank you for your tolerance. Exactly how many people at the FDA are monitoring the dietary supplement industry? How many employees?

Mr. BRACKETT. In total, I do not know the exact answer to that, because many of them in the field—again, I could be happy to get back with you to find the appropriate answer.

Senator DURBIN. Is it a matter of hundreds or dozens or fewer than 20? Just give me a rough estimate.

Mr. BRACKETT. I do not want to speculate. We will find out. It is not probably hundreds, I do not think, but I can find out what the exact allocation of people to this task is for you and get back.

INFORMATION PROVIDED FOR THE RECORD

In Fiscal Year 2003, FDA had 58 people, *i.e.,* full-time equivalents (FTE), in various parts of the Agency, monitoring the dietary supplement industry.

In Fiscal Year 2004, 59 people (FTE), in various parts of the Agency, were monitoring the dietary supplement industry.

Senator DURBIN. Thank you very much, Mr. Chairman.

Senator VOINOVICH. It is my understanding that if a manufacturer has a defective product, they have the ability to recall this product. I am not sure if there is a law that requires manufacturers to report the defective product, or they are doing it because they want to protect themselves from a lawsuit. Would it not make sense to make it mandatory for these companies to submit adverse event reports?

Mr. BRACKETT. Well, again, that would be one thing that could be done, but again, that is just a small part of the whole or at least an equal part of the many different factors that would factor in. So if we were to have adverse event reporting mandatory, and right now, the administration has no position on this, again, that would not solve the whole problem. We would still need to look very closely at the science, at our knowledge of what has been done pharmacologically, many other things.

Senator VOINOVICH. You said that with the new ingredients, they have to submit it so that you can look at the product, or if that is mandatory, and if they do not do that, then, they can be prosecuted.

Mr. BRACKETT. They are in violation, yes.

Senator VOINOVICH. Subject to penalties, right.

Would it not make a lot of sense to make it mandatory that they at least report these adverse events and provide a penalty that says if they do not do it, they are subject to the same kind of sanctions or worse or whatever that you have on not submitting a product for review prior to putting it on the market if it is new ingredients?

Mr. BRACKETT. Well, that would be helpful, but again, that is not the whole story. And another difficult part of that is many of the dietary supplements today are a combination of many ingredients, unlike many of the pharmaceuticals. So quite often, when you have an adverse event reported, it may not necessarily be caused by the ingredient that you think it is. So it is complicated.

Senator VOINOVICH. When ephedra came out on the market there were some incidents that were claimed to be as a result of taking ephedra that might have been due to something else. It seems to me that even if the event reports showed that the incidents were not caused by ephedra that you would investigate ephedra further.

Mr. BRACKETT. Oh, absolutely. When we have adverse events reports, we do look into it. But again, standing on the pillars of the pharmacology, the evidence-based research, the scientific literature, all of that has to stand together.

Senator VOINOVICH. Well, my common sense tells me that it would be good if we required them to do it. And I think it would probably be very helpful to you also. I suspect that some manufacturers who did have adverse event reports did not submit them to you.

Additionally, I am concerned with people mixing over-the-counter medicine or prescription drugs with dietary supplements. As you know this is a growing industry and consumption is only going to increase. In 2006, 680,000 people in Ohio are going to start getting prescription drug coverage to improve their quality of life. Is there a concern within the FDA that the mixing of prescription drugs and dietary supplements could cause adverse effects?

Mr. BRACKETT. Well, certainly, Mr. Chairman, that is a concern, and that is one of the recommendations we always make is that patients discuss their medications and any other foods as well as dietary supplements that they may be consuming.

Senator VOINOVICH. I take coumadin, and in the disclosure that comes along with coumadin, they talk about vegetables that are strong in vitamin K, and if you consume high levels of vitamin K, it could make the drug less effective.

It would seem to me that a dietary supplement, should carry the same type of information. Individuals ought to be informed that if they are taking a drug like coumadin, a blood thinner, that these kinds of interacting could dilute the product, and therefore, the drug they are taking may not be as effective as it should be.

Do you think the dietary supplement should be required to put the same kind of warnings on their labels?

Mr. BRACKETT. Well, I think that would be good for them to do if they knew what the interactions were. Quite often, the manufacturers of the drugs have a better understanding of what interactions have been studied in much more depth.

Senator VOINOVICH. You have to wonder how much real thought is going into labeling dietary supplements.

One reason for such huge growth in the dietary supplement industry is the ability to purchase them over the Internet. Many of these supplements have big claims on their Websites.

Mr. BRACKETT. Well, I agree. And this goes back to my earlier statement. We simply have to know more about the ingredients we are taking, and that is why we do appreciate our colleagues at the University of Mississippi and at the National Institutes of Health actually doing research on both the properties of these ingredients and the beneficial aspects of the ingredients as well.

But again, one of the issues that we have to deal with is finding out exactly what the ingredient is in the first place, and sometimes, that is the first challenge.

Senator VOINOVICH. Senator Durbin.

Senator DURBIN. Dr. Brackett, when Dr. McClellan was Commissioner, he promised enforcement action against some of the ephedra substitutes. This product here, Stacker-2, which is advertised on television, this is now advertised as ephedra free, and if

you will look at the operative ingredients, they include cola nut and citrus aurantium, which is also known as bitter orange.

Now, Dr. McClellan said that he was going to take enforcement action against products containing bitter orange and usnic acid, which are now ephedra substitutes. Can you tell me what has been done so far in that enforcement action?

Mr. BRACKETT. Sure, actually, what Dr. McClellan's intent was anything, any of those stimulant products that were to be used in place of ephedra were to get a much closer scrutiny to find out, in fact, if they were of danger, and that is something that we have been doing. We have been looking at ephedra substitutes; again, to characterize them, to find out specifically what is in the products that are on the market; in some cases, you may have parts of dietary supplement come in from one part of the plant versus another part of the plant, and they may have different amounts entirely of, in this case, citrus aurantium. So we are trying to get all of the scientific data that we need, and if it looks like there is something that is at risk, we will take action.

Senator DURBIN. This is an unusual assignment for the FDA, because when it comes to other products that you monitor, for instance, prescription drugs, is it not true that the burden is on the manufacturer of the drug to establish its safety and efficacy, and in the case of dietary supplements, we are talking about the FDA scrambling to find the personnel, the time and the resources to do the research on the product that is already on the market; is not that true?

Mr. BRACKETT. That is true. This is a little bit different than pharmaceuticals. In this case, the law is almost ahead of the science. In the case of pharmaceuticals, they are specifically developed with a chemical structure that people know about. In this case, people are taking common ingredients for which we often do not understand what the active ingredient in it is. And so, it is taking some basic research to just define and characterize what the products we are dealing with are.

Senator DURBIN. We are trying to take a look back at DSHEA, and as you take a look back, is not this an extraordinary if not impossible burden for the FDA to handle, to try to look at each new ingredient and then try to do enough research to determine that even on the market, it is not dangerous?

Mr. BRACKETT. Well, it is impossible for FDA to do. This is why we partner with NIH. There are specifically in DSHEA the Office of Dietary Supplements that was established to help with this in addition to our academic partners as well. So it is a large-scale effort.

Senator DURBIN. Do you have the specific responsibility within FDA for monitoring the dietary supplement industry?

Mr. BRACKETT. We have the specific authority, yes, to oversee the dietary supplement industry.

Senator DURBIN. And as the director of the Center for Food Safety and Applied Nutrition, that is your responsibility.

Mr. BRACKETT. That is correct.

Senator DURBIN. I mentioned the article in *Oprah Magazine* about specific problems, and you said you were familiar with it. Is this the kind of thing, having been brought to your attention, that

would result in activity by the FDA to establish whether or not the assertions in here are true and that some products currently on the shelf are dangerous?

Mr. BRACKETT. Yes, and in fact, this article was brought to my knowledge by my staff who, in fact, is actually checking into those assertions.

Senator DURBIN. And let me ask the same thing about the Consumer Reports story. This Consumer Reports story from May of this year lists some 12 different supplements, starting with some that they have identified by testing as definitely hazardous to likely hazardous. Have you undertaken in the FDA any kind of investigation or study of these dietary supplements which have been identified as dangerous?

Mr. BRACKETT. Yes; in fact, much of the information in the Consumer Reports article was not new to us. We did know about that. We have, in fact, done some surveillance since that time to look for certain ingredients that were listed in there as well so——

Senator DURBIN. Have any of these products been taken off the shelf, like ephedra?

Mr. BRACKETT. Well, ephedra has been off, unless it is there illegally.

Senator DURBIN. Any other products on the Consumer Reports list?

Mr. BRACKETT. We have listed or sent out warning letters, for instance, for aristolochic acid. In fact, that was one of the items for which we did surveillance and to this point have not found them in products marketed as dietary supplements.

Senator DURBIN. Let me just conclude, Mr. Chairman, by thanking you and also to say this: If the object of this law is to protect American consumers, I think it fails on its face. Take a look at the obvious here: 10 years after passing the law, we still have not established standards so we can even identify what is in these products. And I think, by the nod of the head, you agree with me. We do not know what is in them, to start with. We do not know if it is 4,000 IUs or 3,000 IUs. We have no idea whether there is lead contained in multivitamins or not.

That is a starting point. The second thing we have not established is the responsibility of the industry. Ten years after the law is passed, we have not come up with a list of pre-1994 ingredients. And even if we did, you have conceded in your testimony it is of little value, because a combination of old ingredients could be dangerous, as dangerous as any new ingredient.

And finally, we do not have any requirement that these companies selling products worth lots of money to them in profits even report to the Food and Drug Administration when people get seriously ill from having taken these products. So that is why I am kind of troubled by your conclusion. Having said these things, having heard these things, you have concluded by saying and therefore, we do not want to change the law.

How can you possibly meet your responsibility to consumers to say to them if you buy a dietary supplement for yourself or somebody in your family, it is safe? How can you meet that responsibility with a law that is so weak?

Mr. BRACKETT. Well, the safety and health of the consumers is our utmost concern. That is the thing that we most want to protect. What we are doing is trying to work, to maximize our activities under the current DSHEA before we would go out and sort of look for new authorities. There are many parts of DSHEA that we think have not been explored, that we can use to protect the public, and that is one of the things that we are going to do, which is why we do want to use DSHEA to its maximum, completely.

Senator DURBIN. Dr. Brackett, that approach is so timid that even the industry is ahead of you. We are going to have testimony later from someone from the dietary supplement industry. They have conceded that adverse event reporting is necessary. And yet, you are afraid to say those words. I think we are in trouble here. I think your watchdog responsibility includes being ahead of the problem and not behind it. If you are stuck with this 10-year-old law that is so deficient, you are never going to get ahead of it.

Thanks for your testimony.

Mr. BRACKETT. Thank you.

Senator VOINOVICH. Thank you. I would like to make one point, and that is I would like to have, in writing from you, the chronology of going forward with this rule for these GMPs. I cannot believe that it has taken that long for it to happen. This law passed 10 years ago, and it is unacceptable.

Mr. BRACKETT. We will be happy to provide that.[1]

Senator VOINOVICH. Unacceptable that it takes 10 years to get something done. I would like to have some assurance from you today this is going to get done at least by the end of this year.

Mr. BRACKETT. We will do our very best to get it done as soon as possible. That is our goal.

Senator VOINOVICH. Is the problem that you do not have enough people?

Mr. BRACKETT. Well, the problem has been partly going through many of the comments that we have to address, as you know, in rulemaking.

Senator VOINOVICH. I would like to know how many people you have working on this. I also would like to know what other responsibilities that you have? So often, we ask agencies to do work, and then, we do not provide them the resources necessary to get the job done. So often we pass the law and forget about the fact that it has to be enforced.

I am really interested in knowing, in getting a candid appraisal from you whether or not you have the number of people you need to get the job done in your agency to implement these laws that we have passed over the years.

Mr. BRACKETT. We will be happy to get that to you.

INFORMATION PROVIDED FOR THE RECORD

Approximately five full-time-equivalent employees (three people full-time, two people at 75 percent, one person at 50 percent) and approximately nine others as necessary, are working on preparing the final rule for publication with dietary supplement GMP's as their first priority. We are also soliciting input on development

[1] The information entitled "Time Line of Activities To Establish Current Good Manufacturing Practice Regulations (CGMPs) for Dietary Supplements," submitted by Mr. Brackett appears in the Appendix on page 70.

of the final rule from two external expert consultants and one GMP expert in FDA's Center for Drug Evaluation and Research (CDER). In addition, when the final rule has been drafted, there will be additional people involved in the review/clearance/publication process.

Over 400 comment letters, approximately 1,600 pages, were received on the proposal, most of which raised substantive issues that need to be addressed in the preamble to the final rule. Accordingly, the bulk of the effort is in reviewing and responding to the comments.

CFSAN, in conjunction with the Agency's field staff, regulates 80 percent of the nation's food supply and is responsible for protecting the public's health by ensuring that the nation's food supply, except for meat, poultry and certain egg products which are the responsibility of the Department of Agriculture, is safe and secure, and honestly labeled. CFSAN has similar responsibilities for cosmetic products. Attached is a May 4, 2004, transmittal letter to our Colleagues in the FDA Foods Community forwarding our projected workload for Fiscal Year 2004 in accordance with the Agency's Strategic Action Plan. You will note that the plan includes 168 "A-list" goals, of which we anticipate at least 90 percent completion this year.[1]

Senator VOINOVICH. Any other comments, Senator?

Senator DURBIN. No.

Senator VOINOVICH. Thanks very much. We really appreciate your coming here today.

Mr. BRACKETT. Thank you, Mr. Chairman.

Senator VOINOVICH. Our next witnesses to testify are Alice M. Clark, Ph.D., Vice Chancellor for Research and Sponsored Programs, from the University of Mississippi; Ronald M. Davis, M.D., member of the Board of Trustees of the American Medical Association; Charles Bell, Program Director, Executive Office, Consumer Reports; Anthony L. Young, General Counsel, American Herbal Products Association; Bruce Silverglade, Director of Legal Affairs, Center for Science in the Public Interest; and Annette Dickinson, Ph.D., President, Council for Responsible Nutrition.

This is a large second panel, so I would appreciate your adhering to the 5-minute rule. I appreciate you testifying today, and again remind you that your testimony will be made a part of the record along with your written statement.

We will begin the testimony with Dr. Clark.

TESTIMONY OF ALICE M. CLARK, PH.D.,[2] VICE CHANCELLOR FOR RESEARCH AND SPONSORED PROGRAMS, THE UNIVERSITY OF MISSISSIPPI

Ms. CLARK. Good afternoon, Mr. Chairman, and Senator Durbin. My name is Alice Clark. I am Vice Chancellor for Research and Sponsored Programs at the University of Mississippi and a professor of pharmacognosy. I also served as a member of the Committee on the Framework for Evaluating the Safety of Dietary Supplements at the Institute of Medicine and National Research Council.

I am here today to talk about our report, which is entitled "Dietary Supplements: A Framework for Evaluating Safety," which was released in April of this year, and my comments today will focus on some key findings and recommendations of the report.

In 1994, of course, Congress passed DSHEA in order to define FDA's authority to regulate dietary supplements. In the fall of

[1] The information entitled "CFSAN 2004 Program Priorities," appears in the Appendix on page 72.

[2] The prepared statement of Ms. Clark, with attachments, appears in the Appendix on page 75.

2000, the FDA approached the Institute of Medicine with a request to devise a science-based framework that it could use to evaluate dietary supplements under the authority of the current statutes.

In short, DSHEA states that supplements are to supplement the diet and are therefore regulated like foods, meaning that they are assumed to be safe. Many of the products on the market are probably safe. However, to identify and take action on the occasional problem product, the FDA must rely on available evidence to evaluate whether an ingredient poses an unreasonable risk.

According to DSHEA, the agency can act to protect the public's health when an ingredient poses a significant or unreasonable risk.

In this report, we offer a science-based approach that allows the FDA to use available data to better identify supplements of concern and then evaluate the safety of those ingredients. This framework consists of three major steps: Signal detection, an initial review of that signal, and an in-depth evaluation of the ingredient.

In the framework's first step, the FDA becomes aware of a signal, a notification or an event that raises concern about a particular ingredient. In the framework's second step, that signal is reviewed to determine if the ingredient should be investigated further. And in the framework's third step, the totality of available scientific data is evaluated to determine if the ingredient poses an unreasonable risk.

This approach works within the parameters of the current law governing how dietary supplements are regulated. One of the key points of this report is that the FDA does not have to find direct evidence of actual harm from use of a supplement ingredient to determine that the product poses an unreasonable risk. Another key point of the report is that historical use of an ingredient is often insufficient to demonstrate that an ingredient does no harm.

The report also describes the significance of other kinds of data the agency can use in its safety evaluation, such as data from animal studies, tests done in laboratories or toxicity of similar or related substances. Some of these types of data may be sufficient by themselves for the FDA to determine that a supplement ingredient poses an unreasonable risk.

With the approach devised by the committee, it is possible for the FDA to conduct effective safety evaluations within the current regulatory framework. However, in the process of devising this approach and reviewing the science, the committee noted that constraints imposed by aspects of DSHEA limit the agency's ability to conduct these evaluations as effectively and efficiently as possible.

We have recommended some changes that could mitigate these constraints and make the law more effective in meeting the goal of protecting public health. I will mention just a few of those key recommendations now: For example, we recommend that supplement manufacturers and distributors be required to notify FDA about health problems that they discover related to the use of their products, and recognizing that other parties also bear responsibility for ensuring that health problems related to supplement use are brought to the FDA's attention, we recommend that health professionals be educated about ways to report health concerns and encouraged to use them.

We also recommend that the toll-free number for FDA's Medwatch be printed on all supplements' packaging so that consumers have a clear way to relay any health concerns. And finally, while the committee did not do a cost analysis of implementing the framework, we recognize that implementing any framework will require additional resources. Therefore, we recommend that FDA be provided adequate resources to implement the framework and more effectively protect the public's health.

Thank you for the opportunity to address you on this important topic, and I would be pleased to answer questions.

Senator VOINOVICH. Thank you. Dr. Davis.

TESTIMONY OF RONALD M. DAVIS, M.D.,[1] MEMBER, BOARD OF TRUSTEES, AMERICAN MEDICAL ASSOCIATION (AMA)

Dr. DAVIS. Chairman Voinovich, Ranking Member Durbin, good afternoon. My name is Ron Davis. I am a preventive medicine physician from Detroit and a Member of the Board of Trustees of the American Medical Association.

On behalf of the AMA, I am pleased to be here to discuss the dangers of dietary supplements and whether DSHEA is working. The AMA has been concerned for years about the use and abuse of dietary supplements. These include herbal products and those containing anabolic steroid-like ingredients and their precursors. Precursors are substances that the body can convert into testosterone or other anabolic steroids.

DSHEA does not provide FDA with enough authority over dietary supplements to adequately protect consumers. What are the problems with DSHEA? First, DSHEA treats a wide variety of so-called natural substances as foods, but the fact of the matter is that herbal remedies, anabolic steroids or their precursors are not foods, and neither are megadose vitamins.

These supplements are biologically active compounds that act like drugs. They also have risks and side effects that can be serious and, unfortunately, sometimes fatal. Therefore, many dietary supplements are really drugs.

Second, because existing law treats these products as foods, people think they are safe. In fact, surveys show that most consumers believe that these products have been approved by the government. But such protections do not exist for dietary supplements. Prescription and over-the-counter medications must be proved safe and effective and receive FDA approval before being sold. There is no such approval for dietary supplements.

For the most part, supplement manufacturers do not have to provide premarket data to FDA: No safety data, no efficacy data, no quality data. They do not have to include warnings, precautions or side effects on their product labels, even for products with known serious hazards. So consumers are not told that many supplements can counteract their prescription medications or cause adverse reactions.

Manufacturers also do not have to provide adverse event reports to the FDA. The bottom line? Consumers cannot be sure that die-

[1] The prepared statement of Dr. Davis appears in the Appendix on page 85.

tary supplements work, are safe and that the bottle actually contains what the label says it does.

Third, under DSHEA, the burden is on the FDA, not the manufacturer, to prove that a dietary supplement is unsafe or adulterated. This is very difficult. Ephedra is probably the best example of how hard it is to regulate unsafe dietary supplements. Ephedra causes a number of well-documented adverse reactions, including heart attacks, strokes, seizures, and death.

For several years, the AMA asked FDA to ban ephedra products from the U.S. market. Yet even for a substance as dangerous as ephedra, it took FDA 7 years to ban the product. Although ephedra has been banned, we are concerned about other dietary supplements containing so-called natural stimulants that still are being sold. These products, labeled ephedra-free, often contain bitter orange, as you mentioned, Senator Durbin. Bitter orange contains ephedra-like substances and may be associated with high blood pressure, irregular heartbeat, heart attack, and stroke.

My written statement provides additional examples of the dangers of other supplements.

The AMA has supported changing DSHEA for the past 6 years. Many dietary supplements, especially herbal products, need to be regulated like drugs. We urge Congress to make four changes in the law: (1) Require premarket approval by FDA of all dietary supplements for evidence of safety and efficacy. As with drugs, manufacturers should have the burden of proving their products are safe and beneficial.

(2) Require dietary supplements to meet U.S. Pharmacopeia standards for identity, strength, quality, purity, packaging and labeling. (3) Require manufacturers to monitor their products for safety and to submit adverse event reports to FDA. And (4) reclassify dietary supplements that contain anabolic steroids or their precursors as drugs, subject to the Controlled Substances Act.

The AMA supports pending legislation such as S. 1722, sponsored by you, Senator Durbin. We were pleased that last week, the House of Representatives passed, by an overwhelming margin, H.R. 3866. We encourage the Senate to pass its companion bill, S. 2195. These bills would make some of the changes that we have recommended.

We appreciate the opportunity to present our views.

Senator VOINOVICH. Thank you, Doctor. Mr. Bell.

TESTIMONY OF CHARLES W.F. BELL,[1] PROGRAM DIRECTOR, CONSUMERS UNION OF U.S., INC

Mr. BELL. Good afternoon, Chairman Voinovich, Ranking Member Durbin and other Members of the Subcommittee. I am Charles Bell, Programs Director for Consumer's Union, the nonprofit publisher of Consumer Reports and consumerreports.org.

Since 1936, our mission has been to test products, inform the public and protect consumers, and today, I offer this testimony on dietary supplements as part of our consumer protection function.

The Dietary Supplement Health and Education Act of 1994 has opened the floodgates to thousands of untested dietary supplement

[1] The prepared statement of Mr. Bell appears in the Appendix on page 92.

products. While many dietary supplements including most vitamins and minerals taken within recommended limits are generally safe and can have important health benefits for consumers, there is a significant and growing number of highly questionable products that would probably not be allowed on the market if they were subject to premarket safety testing.

As has been noted, under DSHEA, the burden of proof for removing unsafe products has been inappropriately shifted from manufacturers to the government. As former FDA Director David Kessler has stated, Congress put the FDA in the position of being able to act only after the fact and after substantial harm has already occurred.

In the aftermath of DSHEA, new dietary supplement products can be introduced overnight, as can novel combinations of new or existing supplement ingredients. Further, unsafe dietary supplement products can remain on the market for many years, in the same stream of commerce as products approved by the FDA as safe and effective for their intended use.

As an example, in 1995, Consumer Reports published this list of five supplements that, according to FDA, could cause serious harm to consumers: Ephedra, chaparral, comfrey, lobelia and yohimbe, and 9 years later, ephedra is the only one of these supplements that has finally been removed from the marketplace, many years after the FDA received reports of serious consumer health problems, including deaths and disabling injuries. But the other four hazardous supplements that we named in 1995 are all still being marketed and sold in retail stores and on the Internet.

In May 2004, Consumer Reports published a major article called "Dangerous Supplements Still at Large" with a new, more comprehensive list but not necessarily exhaustive list, but this includes 12 hazardous dietary supplements including the four herbs earlier named that we believe are too dangerous to be on the market based on government warnings, adverse event reports and medical experts.

These dirty dozen unsafe supplements, which we purchased in stores and online in February, include aristolochia, an herb conclusively linked to kidney failure and cancer; yohimbe, a sexual stimulant linked to heart and respiratory problems; chaparral, comfrey, germander and kava, all known or likely causes of liver failure; and bitter orange, its ingredients having effects similar to the banned weight loss supplement ephedra.

The potentially dangerous effects of most of these products have been known for more than a decade, and at least five of them have been banned in Asia, Europe, and/or Canada. Now, we believe that consumers want additional protections to ensure that supplements are safe. Last month, Consumer's Union conducted an online survey of a random sample of over 1,200 adults regarding dietary supplements as part of a regular national consumer survey that we perform.

The survey found that more than eight in ten respondents agreed that poor regulation of supplements posed a personal risk to themselves and their families. More than nine in ten want the sale of supplements to be conditioned on safety and efficacy. Virtually everyone, 96 percent, agreed that supplement producers should be re-

quired to report adverse events, as is required for prescription drugs.

Similarly, 96 percent want product risk information to be included on dietary supplement labels, and fewer than one in five respondents feel that supplements are already sufficiently regulated.

The current serious gaps in consumer protection in DSHEA are not in the interests of dietary supplement consumers. Consumers turn to dietary supplements because they think these products will promote health and wellness. So it is very important to ensure that these products are safe and do not themselves pose serious health problems.

We are pleased that the FDA finally did take action to remove ephedra from the marketplace in January 2004, finally coming off in April, but we are very concerned that the action came too late for many consumers, who experienced unacceptable health damage, including stroke, seizures, heart attacks, and deaths. And despite numerous warning signals, the agency failed to take action in a timely way to remove that product from the marketplace.

Ephedra is a poster child for a failed policy. We need to understand why the signals of an urgent public health problem failed to trigger prompt action by the Federal Government.

Many consumers are surprised to learn that the government does not evaluate the safety of dietary supplements before they are sold. Joseph Levitt, who was the Director of FDA's Center for Food Safety and Applied Nutrition, has testified that the current regulation of dietary supplements is, for the most part, a postmarketing program, but we cannot even run the postmarketing aspect of that program effectively without the authority to require mandatory reporting of adverse events, and we find this to be one of the most disturbing aspects of the entire ephedra debacle.

The fact is that voluntary reporting of adverse events by manufacturers has failed. From 1994 to 1999, fewer than 10 of the 2,500 reports that the FDA received about serious consumer health complaints actually came from manufacturers, and we are very concerned that evidence has emerged that at least two manufacturers suppressed thousands of adverse event complaints relating to supplements containing ephedra: Metabolife and E'ola, as detailed in my written testimony.

We wonder as we sit here today what else manufacturers may have known about the dangers of ephedra and other supplements, including those on our dietary dirty dozen list. Unless Congress acts now to tighten requirements from adverse event reporting by manufacturers, FDA will continue to lack vital information that is needed to ensure the safety of dietary supplements.

So we would recommend that Congress make appropriate modifications to DSHEA to create a sensible preventive safety system that ensures that supplement products are reviewed for safety prior to marketing and sale. The safety system should also include effective postmarketing surveillance so the government can take prompt safety actions as needed, including recalls, warnings and import alerts. Labels of dietary supplements should clearly indicate what and how much is in the package and provide explicit warning of possible adverse effects, including herb-drug interactions.

We strongly support the provisions in the Durbin bill, the Dietary Supplement Safety Act of 2003, S. 722, that would enable the FDA to take unsafe products off the market more quickly. We also strongly believe that dietary supplement makers should be required to report adverse events to the FDA. And in particular, on this point, I would note there is broad consensus among many parties that adverse event reporting is critical to ensuring supplement safety. As the Institute of Medicine in April urged Congress to amend DSHEA to require mandatory reporting; the AMA supports this position; the Inspector General of the Department of Health and Human Services has called for it. Even Secretary of Health and Human Services Tommy Thompson stated in his press conference in December it would be nice to have the authority to require mandatory adverse event reporting.

And so, we think that is a critical step for us to take to learn from the experience with ephedra.

Thank you, and I look forward to the opportunity to respond to questions.

Senator VOINOVICH. Thank you very much. Mr. Young.

TESTIMONY OF ANTHONY L. YOUNG,[1] GENERAL COUNSEL, AMERICAN HERBAL PRODUCTS ASSOCIATION

Mr. YOUNG. Chairman Voinovich and Ranking Member Durbin, my name is Anthony Young. I am General Counsel to the American Herbal Products Association or AHPA. I appear here because AHPA's president, Michael McGuffin, who was here 2 years ago, had a preexisting commitment with the FDA's Food Advisory Committee.

AHPA's prepared testimony addresses in some detail the issues you have raised with respect to the purpose of this hearing. With respect to FDA and DSHEA, AHPA is pleased with FDA's recent dietary supplement regulatory activities. Under the leadership of Dr. Mark McClellan, FDA began seriously to enforce DSHEA, and these efforts are detailed in enforcement reports found on FDA's Website and in Dr. Brackett's testimony today.

In addition, FDA has now come to closure on how to regulate ephedrine alkaloid-containing dietary supplements and androstenedione, and they have done so. All of these enforcement activities were supported by the supplement industry's effort to assure that the funds necessary for dietary supplement enforcement were earmarked in FDA's budget, and that was a unified position of the supplement industry that those funds were needed.

In addition to enforcement, FDA proposed last year current GMPs for dietary supplements. AHPA was one of the industry trade associations that presented FDA with an industry draft for GMPs in late 1995. While a long time coming and controversial in part, AHPA looks forward as you do to FDA making Dr. McClellan's 2004 year end deadline for the promulgation of GMP regulations a reality.

It is AHPA's view that DSHEA can be strengthened in one important aspect, and that is with a requirement for serious adverse event reporting for dietary supplements. AHPA's Board of Trustees

[1] The prepared statement of Mr. Young appears in the Appendix on page 105.

reached this conclusion in October 2002, and AHPA petitioned FDA the next year for serious AER reporting regulations. Both Commissioner McClellan and Deputy Commissioner Crawford had said FDA does not have the authority to do this.

Accordingly, the time has come for Congress to provide that authority. Any serious adverse event reporting for dietary supplements should have the same protections for privacy of subjects and reporters and nonadmission of causation that FDA and the law accords to drugs, medical devices and biologics. In addition, FDA needs to fairly report and correct AER information that is demonstrably wrong. All of these protections are detailed in our written statement.

As you both noted earlier, DSHEA treats new dietary ingredients differently than old ingredients. This is the same approach followed by Congress when it passed the new drug approval provisions of the law in 1938, the food additive provisions in 1958 and the medical device amendments in 1976. Dietary supplements with old ingredients, like old drugs, old food ingredients and old medical devices are to be proceeded against under the law's adulteration and misbranding provisions, and these are the tools used by FDA to regulate ephedrine alkaloid-containing dietary supplements.

For new dietary ingredients, DSHEA makes FDA the gatekeeper. Only about 45 percent of the new dietary ingredients submitted to FDA go onto the market. The gate is narrow. The requirements for safety substantiation imposed by the FDA are substantial, and the FDA applies the law to those companies that make the required premarket notification.

But it is clear that FDA needs to monitor the dietary supplement market to enforce this valuable provision with respect to those obviously new dietary ingredients that have not passed through FDA's gate. To do otherwise is unfair and disrespectful of the law. Not enforcing DSHEA's new dietary ingredient provision rewards lawbreakers at the expense of those who observe the law, and this is one of DSHEA's most important provisions.

Let me close by saying that AHPA is committed to providing benefits to American consumers through our members' products. Thank you for the opportunity to appear before you here today.

Senator VOINOVICH. Thank you, Mr. Young. Mr. Silverglade.

TESTIMONY OF BRUCE SILVERGLADE,[1] DIRECTOR OF LEGAL AFFAIRS, CENTER FOR SCIENCE IN THE PUBLIC INTEREST

Mr. SILVERGLADE. Thank you very much, Mr. Chairman and Senator Durbin.

I am Bruce Silverglade, Director of Legal Affairs from the Center for Science in the Public Interest. It is certainly appropriate to review the impact of DSHEA on consumers and discuss the need for reforms such as those included in S. 722. We support this legislation, and we urge that Congress enact it this year.

As I will explain in a moment, however, Congress needs to extend additional protections to consumers that are not included in this legislation.

[1] The prepared statement of Mr. Silverglade appears in the Appendix on page 115.

Dietary supplements can play an important role in maintaining good health and can sometimes provide a valuable adjunct to traditional medical treatment. We certainly recognize that. Unfortunately, the safety and effectiveness of all dietary supplements has not been established, and there are many products which are hazardous or no more than 21st Century snake oil.

The problem stems from the passage of the Dietary Supplement Health and Education Act of 1994, and as it has been said, history repeats itself, so it might be useful to look just for a moment at the history of this law. This is a blowup of the lobbying materials used by the industry in 1993 that urged consumers at health food stores to, "write Congress today or kiss your vitamins goodbye."

These kinds of scare tactics were used by the industry to get consumers to write Congress to persuade this body to enact the Dietary Supplement Health and Education Act of 1994. And the reason I bring it up is because the same tactics are being used today to oppose S. 722.

Here, we have another poster: It asks, "Could these products be banned: vitamin C, multivitamins, calcium?" This is a current poster at health food stores. And as the Senate offices on this Subcommittee and throughout this body receive mail from consumers, I want you to know that the mail is being generated by phony scare campaigns being generated not necessarily by these trade associations testifying here today but by many other segments of the dietary supplement industry.

Now, the problems with DSHEA in the area of safety are rooted in that that Act changed the assumptions we make about the safety of products that FDA regulates. The Act changed the prevailing approach that the FDA takes. Food manufacturers do not have to demonstrate their products are safe before they are sold, so if you are selling lettuce, you can just sell it without FDA approval.

But the manufacturers of food additives, drugs and medical devices must prove that their products are safe before they can be sold. Well, what are dietary supplements more like? Drugs and medical devices or lettuce? I think the answer is obvious. But the problem with the law is that DSHEA regulates these products like this kind of product—lettuce.

Although the FDA still has the authority to take dangerous dietary supplements off store shelves, it must first prove that the product pose a significant or unreasonable risk. Well, that is difficult to do if there is no requirement that adverse event reports be submitted to the agency. Such information is essential to ascertaining whether a product poses a significant or unreasonable risk, especially in the absence of a premarket approval system.

Thus, as a practical matter, the FDA has not been able to effectively utilize the authority granted to it by DSHEA. Consequently, the agency has been forced to rely on woefully inadequate remedies, such as issuing press releases, public warnings, medical alerts, voluntary recall requests, and so forth.

Here is one such effort from 1993. This came from a report FDA issued called Unsubstantiated Claims and Documented Health Hazards in the Dietary Supplement Marketplace. It is out of print (it was issued in 1993), but it is available on the FDA Website as of today.

It lists Yohimbe, for example, as a product that has, in the agency's own words, "health hazards," many different types of health hazards. The supplement bottle I just held up before was yohimbe. We bought it today at a health food store. So more than 10 years later, after FDA is issuing press releases and alerts and warnings, this product is still available. Clearly, a more effective regulatory approach must be found if consumers are to be protected.

Now, we all know that FDA banned ephedra, but as the *Washington Post* stated, DSHEA is truly a "terrible law." The *New York Times* called the ephedra ban "not enough" and urged Congress to, "revise the ill-conceived 1994 legislation." S. 722 would help address some of these problems by requiring that manufacturers report serious adverse reactions to the agency. The legislation would also require agency approval of stimulants, one category of dietary supplements that pose some of the most severe hazards.

These are useful steps, and we support the legislation. But we urge Congress to go further. Safety standards for dietary supplements that are used by children, pregnant women, the elderly, and other vulnerable groups determined by the FDA to be at particular risk should be raised higher than is now provided for in the law, and manufacturers should be required to submit evidence of safety before such products are sold.

These steps, together with the provisions already incorporated in S. 722, would go a long way to ensuring that supplements in the United States are safe. Thank you.

Senator VOINOVICH. Thank you. Dr. Dickinson.

TESTIMONY OF ANNETTE DICKINSON, PH.D.,[1] PRESIDENT, COUNCIL FOR RESPONSIBLE NUTRITION

Ms. DICKINSON. Senator Durbin, Senator Voinovich, thank you for giving us the opportunity to testify here today.

The Council for Responsible Nutrition is a trade association of dietary supplement manufacturers, and I am the president of CRN. Our members include manufacturers and marketers of national brands as well as store brands of dietary supplements available to consumers through the mass market, through natural product stores, direct sales and mail order.

Our members include not only the manufacturers of finished products but also the suppliers of the bulk ingredients such as vitamins, minerals and botanicals that are contained in these ingredients. DSHEA was passed 10 years ago for two reasons: One was to ensure that consumers would continue to be able to choose safe and beneficial dietary supplements of a wide variety of products. The second was to increase the information available to consumers about the purposes and uses of those dietary supplements.

The past 10 years have demonstrated that these purposes are being fulfilled, as are other goals established by the law, which I would like to address briefly. I think it is important to recognize that dietary supplements have always been considered as a subcategory of foods. This official categorization was not, as some of our witnesses would have you believe, created by DSHEA.

[1] The prepared statement of Ms. Dickinson, with attachments, appears in the Appendix on page 123.

In fact, it precedes DSHEA by about 56 years. The Food, Drug and Cosmetic Act of 1938 included dietary supplements within a category of foods called foods for special dietary use. In 1941, FDA established definitions for this category of products, and in 1976, that definition was added to the Food, Drug and Cosmetic Act in Section 411, the vitamin and mineral amendments.

That definition is extremely broad, covering vitamins and minerals but also all "other ingredients intended for use in supplementing the diet." DSHEA reconfirmed that dietary supplements were to continue to be regulated as foods and established a specific definition to clarify the categories of ingredients that were to be permitted in those dietary supplements.

As has already been noted, it grandfathered ingredients that were already on the market at the time the act was passed, just as was done with food ingredients when the food additive amendments were passed and just as was done with old drugs when the drug amendments were passed.

DSHEA grandfathered those ingredients in the same way that this was done in other food categories. At the same time, DSHEA established a premarket notification requirement for new ingredients much in the same way that new GRAS substances (substances generally recognized as safe) put on the market today for use in foods are evaluated by their manufacturers for safety before they are put on the market. There is no requirement for FDA evaluation of new GRAS ingredients.

FDA has been seriously reviewing and evaluating these 75-day notices that have been submitted for these new ingredients, and this is one of the many ways in which FDA under the recent Commissioner, Dr. Mark McClellan and the current acting Commissioner, Dr. Lester Crawford, have been vigorously implementing the act.

As you all know, FDA issued a final regulation this year that banned ephedra in dietary supplements as of April 12, 2004. That rule is currently undergoing judicial review and has survived the first phase, in which the court denied a preliminary injunction. This is generally viewed as an indication that the rule is likely to survive the entire review process.

It is sometimes said that FDA took 10 years to take definitive action against ephedra, but this is not, in fact, an accurate description of the process. From the time former Commissioner McClellan took office and decided to resolve this ongoing issue, which has been a serious problem for everybody involved, for industry, for consumers and for FDA, from the time Commissioner McClellan took office, it took the agency less than 2 years, which, as you well know, is lightning speed in terms of the regulatory process, to issue a final ban on ephedra.

The earlier delays that occurred in FDA enforcement were not due to inadequate authority but were due to false starts, wrong turns and a frank unwillingness to actually use the new provisions of DSHEA that were provided and that were ultimately used as Congress intended.

Another issue that has been troubling to the industry is the issue of andro. CRN and other industry trade associations are supporting Congressional legislation that will place andro on a long list of

similar ingredients that are to be placed under the Controlled Substances Act, which effectively removes them from the dietary supplement category. That legislation passed the House on June 3 and is expected to pass the Senate during this session.

FDA has also taken separate action against andro, as was mentioned here today, sending warning letters to a number of manufacturers arguing that andro is an unsafe ingredient and is, moreover, a new dietary ingredient for which a 75-day notification has not been submitted. Between the Congressional and FDA action, andro should be off the table as an issue of concern by the time the next Congress convenes.

There has been much talk about adverse event reporting. If there were to be an adverse event reporting requirement, it would be important for it to at least contain protections for reporting companies and for individuals that are included in regulations applicable to other FDA-regulated categories, including prescription drugs. The legislative proposals currently on the table tend to actually exceed the requirements that currently exist for pharmaceuticals and thus are not provisions we can support.

We support the need for more resources for FDA to implement the law and are in support of the Hatch-Harkin bill, which would provide FDA with very substantial new resources. We also support——

Senator VOINOVICH. Ms. Dickinson, your time is up.

Ms. DICKINSON. Yes, I am concluding.

We also supported the provisions in DSHEA which created the Office of Dietary Supplements, which the Congress has very appropriately given significant resources.

With all of these changes, Senators, we hope that when you come back in January 2005 to the next session of Congress, we will be able to return to hearing rooms such as this one and discuss the role of dietary supplements in improving the health of the population and ultimately in reducing health care costs.

Senator VOINOVICH. Thank you very much.

According to a recent poll, most Americans believe that dietary supplements are safe and are approved by the FDA before they can be made available to the public.

Should this, in fact, be the case, and do you believe that the FDA's authority to regulate dietary supplements is sufficient to protect the health of the American public? I have heard from all of you that adverse event reports should be made mandatory. What else beyond that? Dr. Dickinson.

Ms. DICKINSON. I would say the primary thing that is needed is exactly what FDA has been doing in the past couple of years, which is to actively enforce and implement the law. I think that it is not possible to say that the law has not worked until FDA has actually seriously attempted to implement it, which they are now doing. And I think they need a little bit more time to demonstrate the effectiveness of that approach, as has been demonstrated in the case of ephedra.

Senator VOINOVICH. I would like to ask the panel the same question I asked Dr. Brackett from the FDA. Is it your observation that the FDA has the resources needed to enforce DSHEA. Dr. Davis.

Dr. DAVIS. Well, our position would be that the FDA does need more resources to address this issue. I think the fact that it took the agency so long to get the ephedra-containing products off the market and the fact that it has taken so long to finalize promulgation of standards for good manufacturing practices are pieces of evidence that the agency is not able to act as promptly and effectively as it could.

Senator VOINOVICH. So even if we did require mandatory adverse event reporting, we have to make sure that they have the people necessary to follow up on the reports, correct?

Dr. DAVIS. That is correct. And sometimes, the agency can work on a problem with in-house staff, and sometimes, it would need to contract out and get some expert assistance from the outside, like in the case of the ephedra study, where they brought in the RAND Corporation.

Senator VOINOVICH. Mr. Silverglade.

Mr. SILVERGLADE. Yes, thanks very much, Mr. Chairman.

It is our position that, of course, while all government agencies could use more resources, we do not like throwing good money after a bad law. And the way DSHEA is set up, and I think the witnesses attested to this, and Senator Durbin's questions to the witnesses illustrated this, is that the burden is on FDA, for example, to investigate each of these market notifications for these new products to determine if the product is safe.

That expense should be borne by the manufacturer and then turned over to the FDA for a quick review by the agency. The whole burden should not be on the FDA. It is extremely costly, and the agency did say about 2 years ago that it would require $90 million over 5 years, I believe, from Congress to fully implement DSHEA. Last year, Congress gave the FDA an additional $1.5 million. That is not anywhere close to the $90 million the agency says it needs to implement DSHEA.

So what should really happen is the law should be changed so that the expense of investigating the safety of these products is put on the manufacturers who profit from their sale.

Senator VOINOVICH. You suggest that before the products be put on the market, the manufacturer has to do the same thing that one has to do with a prescription drug and prove that it is not harmful to the public?

Mr. SILVERGLADE. No, we do not favor an across the board requirement of that sort. Ordinary vitamins and minerals are generally recognized as safe and do not need to undergo an FDA review. On the other hand, a product like this, yohimbe, which is from tree bark, and is known by FDA to be hazardous, this should not be on the market until manufacturers can demonstrate to the agency that it is safe.

The agency itself has said since 1993 that it is unsafe.

Senator VOINOVICH. How do they know that it is unsafe. How does the FDA find out about unsafe products if manufacturers do not have to submit it to the FDA before they can put it on the market?

Mr. SILVERGLADE. Well, on this kind of product, which is an herb, not an ordinary vitamin or mineral, the manufacturers, the

distributors, the sellers of this product should have to go to the FDA first to get approval before selling it.

Senator VOINOVICH. So it is more specific?

Mr. SILVERGLADE. Right; dietary supplements fall into three major categories: There are ordinary vitamins and minerals, which are presumed safe for the most part. There are just one or two exceptions. Herbal products comprise a second category, and then we have a miscellaneous group of products, a third category. These products could be anything from shark cartilage to cow organs, bull testicles; believe it or not, it is all out for sale on the market.

Ordinary vitamins and minerals do not now have to be reviewed by FDA, but products in these other two categories probably should be reviewed by the agency, as the American Medical Association has suggested, before they are sold to ensure that they are safe.

Senator VOINOVICH. You are saying all of them should be or just some of them?

Mr. SILVERGLADE. Just certain categories that are known by the medical community to be more likely to pose health hazards.

Senator VOINOVICH. Are you at all concerned about the outrageous claims that you see on the packaging and advertising of some of these products that lead you to believe that they are going to do this and that?

Dr. DAVIS. Could I comment on that, Mr. Chairman?

Senator VOINOVICH. Yes, Doctor.

Dr. DAVIS. You are referring to structure and function claims, and I think that is an example of how DSHEA is not working. And I just found five products on the market today that are making some rather unbelievable claims, and just to read a few of those: Provides dietary support for a healthy nervous system. Provides dietary support for normal, healthy, cerebral blood vessel tone. Promotes healthy immune system by supporting T and B cell function, protecting against cellular damage and introducing beneficial enzymes. Optimal support for allergies and sinuses. Helps cleanse the liver from impurities in the diet and environment. And then, the last one is, may help manage hot flashes and night sweats associated with menopause.

Now, these are structure and function claims. The manufacturers are required under DSHEA to be able to substantiate the truthfulness of those claims, but they are not required to provide data to the FDA to prove that. They are required to put a disclaimer on the product that says this statement has not been evaluated by the FDA. This product is not intended to treat, cure or prevent disease.

So on the one hand, you have these claims that I just read for you, and then, right underneath, there is the claim that this is not a claim. It is not a health claim; it is a structure and function claim. And can the ordinary consumer distinguish between "a structure and function claim and a health claim?" As I read this as a physician and putting myself in my patients' shoes, those claims that I read sound awfully like health claims, which should put them under the authority of the FDA, and the manufacturers should be required to prove that those claims are correct at their own expense.

Senator VOINOVICH. My time is up.

And I will give you a chance on my next round to—I am sorry. Senator Durbin.

Senator DURBIN. Please let her go ahead.

Senator VOINOVICH. Go ahead, Dr. Dickinson.

Ms. DICKINSON. In response to your question about the claims, it is our belief that false and misleading claims are not only a disservice to the consumer but are actually an unfair trade practice. We worked with the Federal Trade Commission and the FDA to get action taken on coral calcium products a year ago, which were claiming to prevent and treat at least 400 different diseases.

These claims simply should not be allowed on the marketplace. And I think part of the answer to your previous question as well is that industry should be cooperating with FDA, responsible industry should be cooperating with FDA and FTC to see that these issues are taken care of, and that is one of the ways that the resources of FDA can be stretched and made more effective.

Senator VOINOVICH. I will let Senator Durbin take over.

Senator DURBIN. Mr. Young, I want to make sure I understand what your association has decided. You agree, then, that there should be adverse event reporting of all dietary supplement products.

Mr. YOUNG. Reporting of serious adverse events for all dietary supplement products, that is correct.

Senator DURBIN. Whether they are characterized as pre-1994 products or post-1994 products.

Mr. YOUNG. That is correct.

Senator DURBIN. Regardless of combinations, whether they are old or new.

Mr. YOUNG. All dietary supplements, all serious adverse events associated with them.

Senator DURBIN. And I assume from what you have added in your testimony here that you are asking for the same basic protection when it comes to privacy and legal admissions as currently exist on AERs for pharmaceuticals, for example.

Mr. YOUNG. That is correct, Senator.

Senator DURBIN. What is your position on premarket testing of your products, particularly of stimulants?

Mr. YOUNG. I think that our view is that stimulants can be regulated under the current law, and I think we have provided that information to your staff, but we think they can be regulated under current law. FDA has the authority to look into these various ingredients. Some of the stimulants mentioned in the Consumer Reports article have been known about for years.

Our trade association has had positions with respect to the labeling of the yohimbe for a long time. It is set out in the Botanical Safety Handbook. And if these matters rise to a level of concern, FDA has the tools, we believe, to take the action they feel is necessary, whether it is to ban an ingredient, as they did with ephedrine alkaloid-containing supplements or whether it is to require labeling, which is another option FDA has.

Senator DURBIN. Many years ago, when we were having trouble with approval of medical devices, the FDA did not have the resources to approve devices, the industry decided to agree to pay a user fee to the FDA to provide them with the resources and staff

necessary so that these approvals could take place. Is your association prepared to pay a user fee to the FDA to make certain there is adequate review and testing of your products before they are marketed?

Mr. YOUNG. I would assume that you are talking about new dietary ingredients, and let me clarify something that Mr. Silverglade said.

Senator DURBIN. No, I am talking about all.

Mr. YOUNG. All ingredients? No, because I think at that point, with respect to the older ingredients, we believe that they can be assessed under the law; that there is information available on old ingredients, and that FDA has the tools necessary to evaluate that.

Senator DURBIN. Mr. Young, I suspect that we are both doctors of the law. I know I am not a medical doctor; perhaps you happen to have that in your resume. But you heard Dr. Brackett say earlier that even new combinations of old ingredients could be dangerous. So how can you draw this distinction, as the law does, and say that we are going to make this apply only to new ingredients?

Mr. YOUNG. Well, it is a distinction that the law does make, and I think if we can effectively deal with new ingredients under the new dietary ingredient provision, which is a provision where the manufacturer submits the information, by the way, and FDA only evaluates what is submitted, FDA does not go out and do independent research on new ingredients.

The manufacturer must present the data for review, and that data must pass muster or not. But with respect to old ingredients, there is information out there. It is readily available. The Botanical Safety Handbook where we talk about the safety, the cautions, etc., associated with various herbs was not written in a vacuum. There is a lot of information available to FDA and to others to evaluate the safety of these materials.

Senator DURBIN. So, Dr. Davis, if we are talking about old ingredients in the Botanical Handbook, and we are dealing with products that present these ingredients in new concentrations and new combinations, do you accept the premise that they are still benign?

Dr. DAVIS. No, I do not. I think we may discover that there are harms that we did not know about before. There may be new interactions between an old dietary supplement and a new prescription medication that has just come on the market. There may be combinations, as you have pointed out, with an old dietary supplement and a newer one or new combinations. We talked during the ephedra hearings about ephedra being combined with caffeine, for example. So I would not accept that premise.

Senator DURBIN. Let me ask Dr. Dickinson a question, if I might, and I am going to go to your testimony here, because I think you were rather explicit when it came to the issue of ephedra, in which I can find it quickly here. I apologize. I had it underlined. You said delays were due to false starts, wrong turns, and an unwillingness to actually use the provisions of DSHEA as Congress intended when it came to the banning of ephedra, and you credited Commissioner McClellan with having taken control of the agency and, in less than 2 years, as you say, lightning speed in terms of the regulatory process, responded to this issue.

Did you include in your false turns the statement by the largest manufacturer and retailer of ephedra, Metabolife, to the FDA in 1999 that, "Metabolife has never been made aware of any adverse health events by consumers of its products. Metabolife has never received a notice from a consumer that any serious adverse health event has occurred because of ingestion of Metabolife 356?"

A statement by Metabolife in 1999, and then, after lawsuits were filed by the Department of Justice and individuals, here is what came out: Metabolife had deliberately misrepresented this fact to the FDA. Metabolife had 16,500 adverse event reports for Metabolife 356, including almost 2,000 significant cardiac, neurological and psychiatric reports.

So when you are saying the problem was false starts at the agency, and Dr. McClellan finally straightened it out, what kind of responsibility do you accept as an industry for this kind of concealment and obfuscation of adverse event reports by Metabolife?

Ms. DICKINSON. I think this kind of concealment and obfuscation is just as outrageous as you think it is. But this is one company's activities.

Senator DURBIN. The largest company.

Ms. DICKINSON. A large company that is not, in my view, characteristic of the industry as a whole. When I spoke of false starts, I refer to the fact that FDA, after having first started begun to receive reports of adverse events on ephedra in 1993, held two advisory committee meetings, one in 1995, one in 1996, at which they failed to come to a unanimous conclusion about how to act; produced a rule in 1997 which overtly attempted to use the adverse event reports for purposes that FDA has always recognized and still recognizes they cannot be used for.

The Government Accounting Office found that rule to be inadequately supported in terms of the specific actions FDA took. Following that event, FDA then did not take further action until McClellan's action in 2003. So there is a period of time there where FDA started off in one direction, was found not to be on good ground in going in that direction, and it really took Commissioner McClellan to put them in another direction.

Senator DURBIN. That was during the same time that the largest retailer of ephedra products in America was deliberately lying to the Government about adverse events.

Ms. DICKINSON. I understand that, I understand that, and I think it is outrageous.

Senator DURBIN. And that outrage also made it more complicated, did it not, for FDA to evaluate the danger of the product.

Ms. DICKINSON. I do not think it did, and let me explain why I do not think it did. As outrageous as that event was, I think the reality is that FDA knew everything they ever learned about the pattern of events associated with ephedra within the first couple of years that they were receiving adverse events. I think that from a scientific and public health point of view, it is a fact that one does not have to know about every event that occurred in order to understand what pattern is occurring.

There were millions of people using ephedra, and FDA had a very extensive sample of the events that were occurring. I think from a scientific and public health point of view, they knew exactly

what was happening, even if they did not know the actual number. And I think that is the same information that FDA eventually used in finalizing the rule.

Senator DURBIN. I think the fact that it took so long, and so many people died while we were waiting for this to occur is a suggestion about the inadequacy of the law.

Mr. Chairman, I will wait and do another round of questions when you are finished.

Senator VOINOVICH. Is there a fee that a manufacturer must pay when they intoroduce a new ingredient?

Mr. YOUNG. No, Mr. Chairman.

Senator VOINOVICH. So the cost of this is all being borne by the FDA; is that right?

Mr. YOUNG. That is correct. FDA evaluates the data that is presented to them by the company coming to them with the new dietary ingredient.

Ms. DICKINSON. But the company does the work of preparing the data, so they help.

Senator VOINOVICH. The fact is that there is no fee for the FDA to review the data the company prepares. How about prescription drugs? Is it the same situation with prescription drugs? Is there a fee for the FDA to review the data the company submits?

Ms. DICKINSON. With drugs, there is, but not with food additives and not with GRAS ingredients. On the food side, there is no fee associated with the review of a GRAS notification.

Senator VOINOVICH. That is because the definition of a dietary supplement is still in the food category. I got the impression here that it should be defined as something other than a food product.

Ms. DICKINSON. No, absolutely not, not from us.

Senator VOINOVICH. How about the other witnesses?

Mr. SILVERGLADE. Thank you, Mr. Chairman.

I would define it a little differently than a food product. It does not look like food to me.

Ms. DICKINSON. Does saccharin look like food to you?

Mr. SILVERGLADE. It comes from tree bark. I would not eat it as food.

Senator VOINOVICH. Mr. Young.

Mr. YOUNG. There are user fees for new drugs, and there are user fees for medical devices. I do not know the degree to which user fees in this industry would be appropriate. There have only been 188 new dietary ingredient notifications submitted to FDA in the 10 years that this law has been in effect. I think we have a lot greater concern as an industry with those people who are not going through the toll booth and paying the toll or at least gathering the information together and having it reviewed by FDA.

It is like an 8-lane highway with a toll booth on one lane. Responsible manufacturers are going through that door. I do not think they ought to have to pay in order to go there and have a 45 percent success rate of getting through until this agency is able to deal with those who ignore the law entirely.

So I do not believe that it is something that would really facilitate the proper and timely review of these notifications.

Senator VOINOVICH. You are saying 188 in a 10-year period have come through the door?

Mr. YOUNG. That is correct. We believe about 45 percent of those were allowed by FDA to go to market. FDA does not approve; they simply allow these products to go to market without objection.

Senator VOINOVICH. Of the 188 new ingredient projects, only 45 percent were allowed to go to the marketplace?

Mr. YOUNG. That is correct, Mr. Chairman.

Senator VOINOVICH. What percentage of dietary supplement manufacturers are avoiding this requirement that the FDA review their product?

Mr. YOUNG. It is very difficult to say how many there are, but I have been to a lot of trade shows, and I have read trade magazines that can be read by FDA as well, and there are a lot of folks out there offering new ingredients, new, this is the first time ever, and in the enforcement context, my own view is these would be low-hanging fruit, easy targets. And this is an important part of the law to enforce.

Senator VOINOVICH. One problem that I have, whether it is Enron or Global Crossings, is that you have some bad apples out there, and it seems to me that the industry itself, in order to protect itself, should become a lot more aggressive in bringing these matters to the attention of the Food and Drug Administration. How do you feel about that?

Mr. YOUNG. I know it has been done, that these matters have been brought to FDA's attention. I do not know that any of them have been acted upon. However, certainly, it was part of the decision FDA made with respect to androstenedione. FDA said on the one hand, it is not a dietary ingredient at all; it is illegal as a dietary supplement, and second of all, no notification has been filed if it is a dietary ingredient. So you are off the market. That is the only instance I am aware of, and industry and others urged FDA to do that, and it did so.

Senator VOINOVICH. Does your organization, the American Herbal Products Association, take the initiative to police your own industry?

Mr. YOUNG. I think our association has brought matters to the attention of the Federal Trade Commission. I am not certain about the FDA. I know individual competitors in the industry have brought matters to the attention of FDA with respect to new dietary ingredients, and I think it is something that should be done more, because we do have a role, obviously, an important role in protecting the integrity of this industry.

Senator VOINOVICH. Dr. Dickinson, how does your organization feel about acting as a watchdog and trying to police your own industry?

Ms. DICKINSON. I agree with Mr. Young that it is very important for us to be strong in taking some initiatives in self-regulation. CRN has just recently established a task force to look at some of the things that we might do more proactively to address some of these issues.

Senator VOINOVICH. I do not know where this legislation is going. I can tell you one thing that if this bill comes up, I am certainly going to give it a great deal of thought. The fact of the matter is that so often the only reason why we get into legislation is because the industries responsible close their eyes to the problems facing

their industry. I think that you all have to be a lot more aggressive in policing your own industry.

Ms. DICKINSON. Let me say that we have been very aggressive in some of these areas like GMPs. The fact that it has taken 10 years is not because we have not been pushing it. In fact, CRN and the other associations took the initiative in 1995, in just 1 year after DSHEA was passed, of going to FDA with draft language which we had already shared with USP that formed the basis of their——

Senator VOINOVICH. What happened? It does not make sense. It is almost illogical. If you are a member of the public, and it is a requirement of the law, and here, it is 10 years later, and it has not happened? How can you explain that it did not happen?

Ms. DICKINSON. Well, it actually was not a requirement of the law. They were permitted by the law to do this. In the meantime, until we have unique dietary supplement GMPs, we are fully subject to food GMPs, so it is not that there are not any. It is that there is an opportunity to ratchet up the level of quality that would be required, and industry was fully supportive of that. FDA has a lot of stuff on its plate, including the new bioterrorism act, which we have also all had to be complying with and which, in fact, has brought a very significant amount of new resources to the agency which it can use for all of its regulatory activities.

Senator VOINOVICH. So in this case, you would say that because of September 11 and the new additional money that is helping the agency overall, it is not a situation of where they have new responsibilities, but they have been given more money, and therefore, you think that they are better off than they were before.

Ms. DICKINSON. It is a mix, but they got about 700 or 800 new inspectors as a result of the new bioterrorism law. They got requirements for registration. Companies had to register as of December 12 of last year, so they now have resources that they did not have before. There are also provisions related to advance notice of imports and the review of records which strengthen their overall position.

Senator VOINOVICH. Mr. Silverglade.

Mr. SILVERGLADE. Thank you, Mr. Chairman.

With respect to GMPs, it is really kind of a black box. We do not know exactly what happened, but a few things are a matter of record that we do know. One thing we do know is that the FDA sent its proposed rule for GMPs to the Office of Management and Budget for approval on November 8, 2000, right after the election.

After President Bush took office, the proposed rule for GMPs was sent back from OMB to the FDA. Then Commissioner McClellan took charge, but now, we had several more years of delay. So instead of doing a very good job, I would submit that the Clinton Administration had finished the job. Then, the GMP rule was sent back by OMB after the inauguration of President Bush. And then, Commissioner McClellan took several more years dealing with it.

Now, the FDA finally proposed a rule last year. And what is holding it up now? I will give you the answer: The industry. The industry has filed hundreds of comments claiming that this has to be changed, that this provision is too strong, and that provision is too strong, and that is why FDA has not issued a final rule.

Senator VOINOVICH. Senator Durbin.

Senator DURBIN. And that is what Dr. Brackett said, 400 substantive comments. So is it any wonder why this GMP is dragging on as long as it has?

I would like to make sure I understand a few of the things that have been said. Mr. Young, are you saying that in the 10 years of DSHEA, there have been 188 new ingredients submitted to the FDA of dietary supplements?

Mr. YOUNG. That is what is noted on their Website. That is correct.

Senator DURBIN. OK; is it correct that there are some 30,000 different dietary supplement products on the market today?

Mr. YOUNG. I have no numbers, but I would not be surprised that is the number of what they call SKUs, the selling units.

Senator DURBIN. That may have been in Dr. Brackett's testimony or in one of the others, but I believe that 30,000 was the number.

Ms. DICKINSON. But the definition——

Senator DURBIN. Excuse me a second, please.

Does not it strike us as odd? Thirty thousand products on the market, and over a 10-year period of time, we average about 19 a year that come before the FDA to test a new ingredient? And going back to Dr. Davis' point, combinations of old ingredients can also raise some concerns here as to new concentrations and new combinations. And I think it is proof positive that this current law is not giving the FDA the authority it needs.

In fact, recall when Dr. Brackett was asked, well, did you have a listing of the old ingredients so you knew where your starting point was? No, it does not exist.

Mr. YOUNG. Well, Senator, the industry did provide lists of old ingredients to FDA. FDA has those lists from the industry. They do not give them legal significance, but I do believe they read those lists when they look at things. There were lists given by, I think, all three of the major trade associations to kind of record, as you suggested earlier, what was in place in 1994.

Senator DURBIN. It also is a fact, is it not, testimony here that fewer than or less than 1 percent of the AERs that have been filed with the FDA came from the industry. Ten out of 2,500, so the voluntary program for dietary supplements to self-report adverse events has generated 10 out of 2,500 adverse event reports in the life of this act.

Is that your understanding, too, Mr. Young?

Mr. YOUNG. I do not know how many have come from manufacturers, but I do not know that there is a voluntary program for manufacturers to send in adverse events other than that FDA would like it. There has been no organized industry activity that I am aware of in that regard.

Senator DURBIN. So how can we take your industry seriously if they do not report products on the market that are causing adverse health events? How can consumers take the industry as seriously interested in the health of America?

Mr. YOUNG. Well, I think the industry evaluates those reports. Our members evaluate those reports, and they make adjustments as necessary in response to those reports. They look at them as signals, and I think one of the reasons we support mandatory adverse

event reporting is so that FDA, with all of its expertise, can aggregate that information and determine whether signals received by one company are similar to those received by other companies and begin with the process that the——

Senator DURBIN. Mr. Young——

Mr. YOUNG [continuing]. IOM has established.

Senator DURBIN [continuing]. How can they aggregate what they never receive?

Mr. YOUNG. They can if there is a mandatory reporting system.

Senator DURBIN. A change in the law.

Mr. YOUNG. That is correct.

Senator DURBIN. Dr. Dickinson, you have said that we should view grandfathering of old ingredients like the grandfathering of food.

Ms. DICKINSON. The grandfathering of GRAS ingredients, which are food additives "Generally Recognized as Safe."

Senator DURBIN. So if we had common foods that cause no problem, and people decided to cook them together, carrots and cauliflower, and that caused no problem, we should not be hauling in the FDA to analyze it. Is that your take on this?

Ms. DICKINSON. With regard to carrots and tomatoes, yes. Not necessarily with regard to the dietary supplement ingredients. In fact, I think it is important to recognize, and I am sure Mr. Young would comment on this as well, FDA, in its review of these new ingredient notifications is, in fact, doing some of the things that you suggest. FDA is determining, on the basis of concentration, different types of extracts, different types of processing, that certain ingredients that companies might have thought were old ingredients are, indeed, new ingredients.

Senator DURBIN. How many old ingredients are there? How many are we talking about?

Ms. DICKINSON. I think we are talking about several thousand. I do not think we are talking about 30,000. And the reason for that is that the number of 30,000 was an FDA number that came about when FDA was proposing nutrition labeling, and the cost of that they——

Senator DURBIN. But do you see that if you take several thousand starting old ingredients and consider just combinations, not concentrations, that you could be ranging into the millions of possibilities here?

Ms. DICKINSON. Well, one can speculate about a lot of things. A large number of those ingredients are essential nutrients or recognized nutrients. A large number of the additional ones are the chemicals that are reviewed in a large number of monographs published by organizations like USP and WHO.

Senator DURBIN. OK; let us start with citrus aurantium, the most popular, I believe, substitute for ephedra. I wrote to the seven largest dietary supplement companies and asked them: Did you test your citrus aurantium product before you marketed it? How many do you think tested it ahead of time?

Ms. DICKINSON. How many of them responded?

Senator DURBIN. Well, of those who responded. It is a good point, but how many do you think tested it?

Ms. DICKINSON. None of them may have tested it in the way that a drug is tested, but they certainly had information from their supplier of the ingredient and from other information that——

Senator DURBIN. Sure did. Let me read you some of the replies. NVE Pharmaceutical.

Ms. DICKINSON. Oh, not them; come on.

Senator DURBIN. Robert Ochifento. Are you familiar with him?

Ms. DICKINSON. I am.

Senator DURBIN. OK. He makes this beautiful little product, Stacker-2. He says: "In my experience, it is unusual for companies to conduct in-house testing for nutraceutical compounds." But then, he referred me to a study involving Seville orange juice, a study that had been published in the Journal of Clinical Pharmacology, as evidence that this was not a dangerous product, citrus aurantium.

And so, we contacted the people who actually authored the study, and here is what they said: Mr. Ochifento, president of NVE, making Stacker-2, who says that this study is the reason why he can sell this product safely, "I do not consider our study using Seville orange juice even remotely sufficient to assess the safety of synephrine-containing dietary supplements. If the industry is doing that, then, in my opinion, they are committing an egregious error."

Do you understand that we are not dealing with benign products here?

Ms. DICKINSON. We are not dealing——

Senator DURBIN. Excuse me. I will finish, and then, you get your chance.

We are dealing with products which can be in lethal concentration with no testing, going on the market making the consumer walking into that store the laboratory test rat. Now, is that what you want to see in the America that you live in?

Ms. DICKINSON. No, it is not.

Senator DURBIN. Is that where you think the FDA should be in allowing these products to be sold without testing, without review of adverse events? You think they should be grandfathered and treated like food. I do not believe that this is a food situation.

Ms. DICKINSON. I think that this is also not a responsible company and a responsible individual that we are referring to here. The fact that this guy does not know one end from the other does not necessarily mean that other companies in the industry do not have better information about these products.

Senator DURBIN. Would you like to give us a list of those companies that we should not buy products from?

Ms. DICKINSON. I would love to, but I do not think I can. I do not think my counsel will allow me to do that.

Senator DURBIN. Well, that sure is reassuring.

Ms. DICKINSON. I certainly can provide you a list of our members, and I think you can be perfectly confident buying from these members or from members of Mr. Young's association or some of the other major associations.

Senator DURBIN. Well, Mr. Young, it turns out that NVE is a member of your association. So what do you want to tell us about him?

Mr. YOUNG. I believe they are a member of our association, and I believe they are the ones that have challenged the FDA's ban on ephedrine alkaloid containing dietary supplements. I have not seen that letter before. I am surprised at his response.

Senator DURBIN. Would the word troubled also be included?

Mr. YOUNG. Troubled?

Senator DURBIN. Are you troubled by his response?

Mr. YOUNG. Yes, because there is a lot more information, I think, available about citrus aurantium, about the—there may be other ingredients that are in that product. I do not know how that product is labeled. There are various cautions that are recommended for these kinds of products or ingredients.

Senator DURBIN. Well it has been labeled by a lawyer for a cure, because it says this product is not intended to diagnose, treat, cure or prevent any disease.

Mr. YOUNG. Well, that is the statement for structure and function I think for the FDA that—but also, there may be cautions on there as well.

Senator DURBIN. It is also pictured on cable, because it is the world's strongest fat burner. How about that?

Mr. Chairman, I think we have achieved what we wanted to in this hearing. Although it has taken awhile, I think we have reached the point where it is clear that DSHEA, which was written 10 years ago as an experiment, is an experiment that has failed the consumers of this country. I do not believe that we collect enough information about these products to say to any unsuspecting consumer of any age in America be safe, by these products.

We have to say buy them at your risk. Your government has not established standards about what is included in the products. We have not established any standards about whether they are lethal, whether they are safe, whether they can achieve the things that they are advertised to do, and we do not even require the makers of the product when they are killer products, causing people's death, to report it to the government.

We have failed miserably, and to think that the FDA's testimony today is that they are satisfied with this law and see no need for change is troubling to me. I think we have a greater responsibility, and I thank you for this hearing.

Senator VOINOVICH. You are more than welcome, Senator Durbin, and I am pleased that you asked me to hold this hearing today. I have learned a great deal, and I am just as concerned about this issue as you are.

I would like to reiterate that the responsible organizations that are represented here and some that are not should take very seriously the fact that this hearing has been held. They need to start doing a better job of policing their own industry.

Last but not least, I do not know if this hearing is going to be on C–SPAN or not, but I can assure you that if it is, the people watching this are going to be a lot more reluctance to purchase any of these dietary supplements because of the information that has been brought out today at this hearing.

I am personally very concerned about this, because I had a brother who took all kinds of dietary supplements and kept urging them upon me. He died from a massive stroke 2 years ago. I am not say-

ing these supplements caused his stroke but there is reason to be concerned. I think there are a lot of Americans out there that for one reason or another think that these pills are going to be the thing that is going to keep them going, and they really are not.

Thank you very much.

Senator DURBIN. Mr. Chairman, if I might say before we close, give thanks to the staff people who worked so hard: On your staff, David Cole and our clerk, Kevin Doran, and on my staff, Krista Donohue, Myrece Johnson and Mindy Mannlein. This was a very challenging issue, and they did a great job on it.

[Whereupon, at 4:46 p.m., the Subcommittee adjourned.]

APPENDIX

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

STATEMENT OF

ROBERT E. BRACKETT, PH.D.

DIRECTOR

CENTER FOR FOOD SAFETY AND APPLIED NUTRITION

FOOD AND DRUG ADMINISTRATION

BEFORE THE

COMMITTEE ON GOVERNMENTAL AFFAIRS

SUBCOMMITTEE ON OVERSIGHT OF GOVERNMENT MANAGEMENT,

THE FEDERAL WORKFORCE, AND THE DISTRICT OF COLUMBIA

UNITED STATES SENATE

JUNE 8, 2004

FOR RELEASE ONLY UPON DELIVERY

INTRODUCTION

Thank you, Mr. Chairman for this opportunity to testify before your Subcommittee at this hearing entitled, "Dietary Supplement Safety Act: How is FDA Doing 10 Years Later."

BACKGROUND ON REGULATION OF DIETARY SUPPLEMENTS

Many Americans take some type of dietary supplement, and in many cases, there is either strong or suggestive evidence that many of these vitamins and minerals and other naturally occurring products have important health benefits. The Dietary Supplement Health and Education Act of 1994 (DSHEA) (P.L. 103-417) amended the Federal Food, Drug, and Cosmetic (FD&C) Act to set up a distinct regulatory framework for these products in an attempt to strike the right balance between providing consumers access to dietary supplements that they may choose to help maintain and improve their health, and giving the Food and Drug Administration (FDA or the Agency) regulatory authorities to take action against supplements or supplement ingredients that present safety problems, have false or misleading claims, or are otherwise adulterated or misbranded. Although dietary supplements are regulated as foods in that pre-market approval is not mandatory, DSHEA and FDA's implementing regulations establish special requirements for dietary supplements that differ in some respects from those covering "conventional" foods, and that also differ from those that apply to drug products (prescription and over-the-counter).

Congress defined the term "dietary supplement" as a product that, among other things, is intended for ingestion, is intended to supplement the diet, is labeled as a dietary supplement, is not represented as a conventional food or as a sole item of a meal or diet, and contains a "dietary ingredient." "Dietary ingredients" are defined as vitamins, minerals, amino acids, herbs or other botanicals, dietary substances (such as enzymes), and concentrates, metabolites, constituents, extracts, or combinations of the preceding types of ingredients. Dietary supplements may be found in many forms, such as tablets, capsules, liquids, or bars.

LABELING OF DIETARY SUPPLEMENTS

Under the FD&C Act and FDA's implementing regulations, the label of a dietary supplement must bear a statement of identity (product name) that identifies the product as a dietary supplement; nutrition information in the form of a Supplement Facts panel; a list of any ingredients not listed in the Supplement Facts panel; the name and address of the manufacturer, packager, or distributor; and the net quantity of contents. In addition, if the labeling includes a claim to affect the structure or function of the body, a claim of general well-being, or a claim of a benefit related to a classical nutrient deficiency disease, the product must bear a disclaimer stating that FDA has not evaluated the claim and that the product is not intended to diagnose, treat, cure, or prevent any disease. Furthermore, a manufacturer of a dietary supplement making such a claim must have substantiation that the claim is truthful and not misleading and must notify FDA that its product bears such a claim within 30 days of marketing the product with the claim.

DIETARY SUPPLEMENT SAFETY

Statutory Framework

As with most foods, there is no requirement for manufacturers of most dietary supplements to provide evidence of product safety to FDA prior to marketing. Accordingly, FDA regulates the safety of dietary supplements primarily through a post-market evaluation of whether the product is adulterated under one of the provisions of the FD&C Act. However, there is a 75-day pre-market notification requirement for manufacturers or distributors of dietary supplements that contain "new dietary ingredients," those dietary ingredients that were not marketed in the U.S. before October 15, 1994, unless the supplement contains only ingredients that have been present without chemical alteration in the food supply as an article used for food. In its notification to FDA, the manufacturer or distributor of the supplement must submit information, including citation to published articles, that forms the basis for the firm's conclusion that the dietary supplement containing the new dietary ingredient will reasonably be expected to be safe. Unless there is a history of use or other evidence of safety establishing in the labeling that the new dietary ingredient will reasonably be expected to be safe when used as recommended, the supplement is deemed adulterated.

Scientific Research

In order to be informed about the safety of dietary supplements, in addition to assessing known reported adverse events, FDA evaluates published literature, evidence-based reports, and the known pharmacology of a compound in order to assist in the evaluation of dietary supplement products. Collaboration with academic centers such as the National Center for Natural Products

Research (NCNPR), Federal partners such as the National Institutes of Health and the National Center for Toxicological Research, and our consumer and industry stakeholders is important in developing a comprehensive safety evaluation of dietary supplement products. For example, the partnership that FDA has with NCNPR at the University of Mississippi is valuable for finding practical solutions to scientific problems. For dietary supplements containing botanical ingredients, development of such a science base can be especially difficult because of the complexity of the chemicals that make up these products and the variability between one product and another.

CFSAN Adverse Event Reporting System (CAERS)

Adverse event reports (AERs) are an important tool for developing a "signal" which can help FDA to identify potential safety problems with dietary supplements. Last year, FDA's Center for Food Safety Applied Nutrition (CFSAN) put in place the CFSAN Adverse Event Reporting System (CAERS) to monitor adverse event reports for CFSAN-regulated products, i.e. food (including dietary supplements) and cosmetics. Adverse event reporting for dietary supplements is not mandatory. CAERS is a computerized system that records reports submitted voluntarily by industry, health care providers, and consumers. This system started collecting reports after June 15, 2003, and unifies CFSAN's adverse event reporting through one common portal. Future planned capabilities include transitioning data from older systems into the CAERS portal, developing a botanical thesaurus to enable more sophisticated search strategies, and electronic links to other databases such as MedWatch and poison control centers.

DIETARY SUPPLEMENT CURRENT GOOD MANUFACTURING PRACTICES (cGMPs)

Under DSHEA, another important arm of FDA's regulatory and surveillance activities used to help ensure the safety of dietary supplement products is the Agency's authority to promulgate regulations for dietary supplement current good manufacturing practices (cGMPs). Such regulations will help ensure product quality and consistency. FDA published a proposed rule for dietary supplement cGMP on March 13, 2003.

Examples of product quality problems the dietary supplement cGMP proposal would help prevent are: superpotent and subpotent products, wrong ingredients, presence of contaminants (e.g., bacteria, pesticide, glass, and lead), under-filled containers, foreign material in a dietary supplement container, improper packaging, and mislabeling. The publication of the final rule on dietary supplement cGMP remains a high priority for FDA. A 90-day public comment period on the proposed rule was extended 60-days and closed on August 11, 2003. During the comment period, FDA staff participated in two outreach meetings and an FDA-sponsored satellite downlink, as well as three outreach meetings organized by industry groups to ensure that dietary supplement manufacturers (especially small manufacturers) and other interested parties were familiar with the proposal.

Due to the volume of comments and requests by commenters, FDA extended the time period in order to receive additional public comments. We are currently reviewing over 1600 pages of comments, which include more than 400 substantive comments that are being carefully analyzed. We plan to publish a final rule once this evaluation is completed. We recognize the importance

of having dietary supplement cGMP in place and we are moving forward to complete this regulatory priority under DSHEA. This proposed rule, if finalized as proposed, will give consumers greater confidence that the dietary supplements that they choose to use will have the identity, strength, purity and composition that they are represented to have.

CONSUMER HEALTH INFORMATION FOR BETTER NUTRITION INITIATIVE

As part of FDA's efforts on dietary supplements, the Agency has been working to inform consumers about these products and their uses. On December 18, 2002, the FDA Commissioner announced the Consumer Health Information for Better Nutrition Initiative. The focus of this effort is to make available more scientifically accurate information about foods and dietary supplements so Americans know the health consequences of what they consume. This Better Health initiative is designed to foster two complementary goals concerning the labeling of food and dietary supplements:

- encouraging makers of conventional foods and dietary supplements to make accurate, science-based claims about the health benefits of their products, and
- bringing enforcement actions against those dietary supplement marketers who make false or misleading claims.

In a July 10, 2003, status report on the Better Health Initiative, FDA issued interim guidance on a process to review qualified health claims, pending rulemaking to provide for qualified health claims. In addition, the Agency announced enhanced enforcement activity against dietary

supplement manufacturers and others who make misleading claims about health benefits that are not based on science. These enforcement activities are described below.

ENFORCEMENT ACTIONS

At the core of FDA's DSHEA enforcement efforts is our commitment to work with industry in order to encourage the legitimate manufacture, sale, and use of dietary supplements while enforcing the law aggressively against fraudulent product claims and other illegal practices. Dietary supplement enforcement efforts include inspections that have resulted in voluntary compliance, voluntary recalls, warning letters, seizures and injunctions, criminal enforcement, and joint enforcement actions with the Federal Trade Commission (FTC) and the Department of Justice.

FDA shares Federal oversight of dietary supplements with FTC. FDA regulates the safety, manufacturing, and labeling of dietary supplements, while FTC has primary responsibility for regulating the advertising of these products. Over the last few years, FDA and FTC have worked well together to ensure that there is a seamless assertion of our jurisdiction over these products. With the mutual goal of consumer protection, FDA and FTC chair an interagency health fraud steering committee that includes Federal agencies in the U.S., Canada, and Mexico. Also, as part of FDA's effort to curb Internet health fraud, the Agency has conducted several "surfs" to identify fraudulent marketing of health care products over the Internet. These actions were carried out in partnership with FTC and other law enforcement and public health authorities in the U.S. and abroad.

From October 2002 through April 2004, FDA has conducted 224 domestic inspections of dietary supplement manufacturers, issued more than 170 warning letters and "cyber letters" to marketers of dietary supplement products, seized products worth more than $9 million, supervised the voluntary destruction of more than $3 million worth of products marketed as dietary supplements that were promoted with unsubstantiated claims or that were unapproved drugs, and obtained permanent injunctions against 5 firms distributing misbranded or unapproved drugs as dietary supplements.

FDA enforcement has extended to our nation's borders, where we have refused importation for more than 1,500 foreign shipments of potentially unsafe or misbranded dietary supplements offered for entry in the U.S. The Agency's enforcement actions send a clear message that FDA will not tolerate fraudulent practices that victimize or endanger consumers.

As with all of FDA's activities, priorities are established based upon the direct impact upon public health. Products that present a direct health hazard to consumers are the Agency's highest priority, although FDA also proceeds against products that present indirect health threats. When the Agency encounters such products, FDA will use all available civil and administrative remedies to assure that the product is quickly removed from the market. We also aggressively publicize our actions to warn consumers and health professionals about such products. In some cases, the Agency may initiate a criminal prosecution against manufacturers or distributors of violative products.

HIGHLIGHTS OF RECENT ENFORCEMENT ACTIONS

April 2004

Dietary Supplements Promoted Online for Weight Loss

In April 2004, FDA sent warning letters to 16 dietary supplement distributors making false or misleading claims for weight loss products promoted over the Internet. Many of these products claim to block starch, carbohydrates, and fat calories, while maintaining that consumers would lose weight without any changes in lifestyle. For example, some of the product labels have claimed:

- "Eat All You Want! Block the Starch and Lose Weight!"
- "Neutralize up to 66 percent of the starch consumed in a meal."
- "This advanced dietary-fat inhibitor helps block the absorption of fat calories."
- "Take 3 capsules before bedtime. Watch the fat disappear!"
- "Guaranteed to block the breakdown of carbohydrates and simple sugars from being converted into fat."

Consumer Warning on "Street Drug Alternatives"

On April 9, 2004, FDA issued a Press Release warning consumers not to purchase or consume products that claim to provide "safe legal highs" or that are marketed as "street drug alternatives" by Cytotec Solutions, Inc., of Tampa, Florida. The April 9th warning expanded on the February 2004 warning concerning a product called Green Hornet, also marketed by Cytotec Solutions, Inc. The products included in this warning were Trip2Night, Invigorate II, Snuffadelic, Liquid Speed, Solar Water, Orange Butterfly, Schoomz and Green Hornet Liquid. The labeling for these products lists a variety of herbal and other ingredients but is incomplete or inaccurate

because it does not provide either the name of the manufacturer or the presence of these active drug ingredients.

By way of background on this product type, in 2001, FDA brought a seizure and injunction action against purported supplement firms, Hit Products, Inc., and Organic Diversions, Inc. that marketed products as alternatives to illegal street drugs. The case, *U.S.* v. *Undetermined Quantities of Articles of Drug, Street Drug Alternatives*, concerned the firms' marketing of products made from a mixture of herbs that promised users effects comparable to illegal street drugs. FDA seized these street drug alternatives as misbranded and unapproved new drugs in violation of the FD&C Act. FDA also sought the destruction of the seized goods and an injunction barring defendants from future FD &C Act violations. In granting this relief, the court found FDA's position on street drug alternatives "highly persuasive" and criticized the defendants' characterization of the products as dietary supplements as a "veiled attempt to circumvent" the FD&C Act. The court "declined to carve out a statutory loophole for drug manufacturers attempting to profit from the illegal drug epidemic by masquerading potentially dangerous substances as legitimate dietary supplements."

March 2004

Androstenedione Warnings

On March 11, 2004, the Department of Health and Human Services (HHS) Secretary Tommy G. Thompson announced a crackdown on companies that manufacture, market, and distribute products containing androstenedione, or, "andro." These products act like a steroid once metabolized by the body. As a result they can pose health risks similar to those of steroids. Andro products are generally advertised as dietary supplements that enhance athletic

performance based on their claimed anabolic and androgenic properties to stimulate muscle growth and increase production of testosterone.

As part of the crackdown, FDA issued warning letters to 23 companies asking them to cease distributing products sold as dietary supplements that contain androstenedione. The warning letters notified the firms that they could face enforcement actions if they did not take appropriate actions. The warning letters stated that FDA assumed that each firm had a basis to conclude that androstenedione was a dietary ingredient. If androstenedione is a dietary ingredient, FDA believes that it is also a new dietary ingredient for which a pre-market safety notification is required. Because no such notification has been submitted by any manufacturer or distributor who received a warning letter, these products are adulterated and their marketing is prohibited under the FD&C Act.

Conviction Hadi Ghadour

On March 9, 2004, Hadi M. Ghandour pled guilty to conspiracy to introduce misbranded and unapproved new drugs into interstate commerce, counterfeiting human growth hormone, and conspiracy to distribute a controlled substance. Ghandour owned and operated Genapharm, Inc., a distributor of supplements specifically marketed to athletes to enhance performance.

During investigations, Ghandour and his co-conspirators were found to be selling tiratricol, a potent thyroid hormone and Class I health hazard, as a weight-loss drug. Ghandour and his co-conspirators also sold products to people seeking alternatives to street drugs and a veterinary drug used to de-worm animals as an imitation of MDMA ("ecstasy"), a schedule I controlled

substance. Ghandour also counterfeited the labels for Nutropin AQ, a human growth hormone manufactured by Genentech, Inc., and placed them on vials containing an insulin mixture.

Ghandour was previously convicted of counterfeiting steroids (misdemeanor) in November of 1998. Two of Ghandour's co-conspirators pled guilty in 2003 and received sentences ranging from probation to three years incarceration. Ghandour faces up to 14 years in prison and a $1,000,000 fine.

Consent Decree of Permanent Injunction: Seasilver USA, Inc., and Americaloe, Inc. On March 8, 2004, the U.S. District Court for the Southern District of California entered a Consent Decree of Permanent Injunction agreed to by the U.S. government, SeaSilver USA, Inc., Americaloe, Inc., of Carlsbad, California, and their principals, Bela Berkes and Jason Berkes. In the Consent Decree, the firms and their representatives agreed to stop manufacturing and distributing violative products, including "Seasilver" – a purported cure-all liquid supplement, and to destroy the seized products at their expense under the supervision of a HHS representative within 60 days of posting bond.

This consent decree followed a coordinated effort in June 2003 between FTC and FDA against Seasilver U.S.A., Inc., and Americaloe, Inc., their owners, and two of the companies' principal distributors. On June 16, 2003, at FDA's request, U.S. Marshals seized 132,480 bottles of Seasilver, worth nearly $5.3 million, from Seasilver USA's San Diego headquarters. Under a settlement with the FTC, entered on March 4, 2004, the Seasilver defendants and the individual distributors agreed to pay $4.5 million in consumer redress.

February 2004

Regulation Prohibiting Sale of Dietary Supplements Containing Ephedrine Alkaloids

On February 11, 2004, FDA published a regulation declaring dietary supplements containing ephedrine alkaloids (ephedra) adulterated because such supplements present an unreasonable risk of illness or injury. The regulation went into effect on April 12, 2004. This rule is being challenged in court but remains in effect during the challenge.

Guilty Plea – David Hinkson

David Hinkson, the owner of Water Oz, pled guilty to two FDA-related counts. The firm manufacturers and distributes water-based products, labeled as dietary supplements, and ozone generators and body suits which the firm claimed were effective to treat a variety of conditions such as AIDS (Acquired Immuno Deficiency Syndrome) and cancer. In his plea, Hinkson admitted not labeling his lithium water as a drug, despite making drug claims for the product, not labeling the ozone generators as medical devices, and that he did not have approval to market the devices. Sentencing is set for July 29, 2004.

Consumer Warning: Green Hornet, Promoted as Herbal Version of "Ecstasy"

On February 25, 2004, FDA warned consumers not to purchase or consume a liquid product called Green Hornet. This product is promoted on the Internet, and sold in stores, as a herbal version of the illegal street drug "Ecstasy." FDA considers this product to be an unapproved

new drug since it contains, among other ingredients, the undeclared active ingredients diphenhydramine and dextromethorphan, found in over-the-counter (OTC) drugs.

FDA became aware of reports of adverse events experienced by four teenagers after consuming Green Hornet. The teenagers were rushed to a hospital emergency room suffering from seizures, excessive heart rates, severe body rashes and high blood pressure. The Green Hornet product involved in this case was sold by Kekio, Inc., Colorado Springs, Colorado, doing business as a store called Mind Excursions. The store, which also operates a website, has stopped selling the product.

Consent Decree letter issued: Vital Health

A letter was issued on February 19, 2004, to Vital Health of West Allis, Wisconsin, advising the firm that it was found to be in violation of the court judgment filed against it in 1992. FDA found that the firm was actively promoting the sale of Herp-Eeze and TobacOff, products labeled as dietary supplements but promoted with drug claims.

Seizure: *Musclemaster.com*

On February 5, 2004, the U.S. Marshal, at the request of FDA, seized approximately 925 bottles of ephedra-containing dietary supplements Betatrim, Thermbuterol, and Stacker 2, from *Musclemaster.com* in Northboro, Massachusetts. The complaint alleged that *Musclemaster.com* was making unsubstantiated claims on its websites for the ephedra-containing products. Specifically, it is alleged that *Musclemaster.com* claimed that its products enhanced the athletic and muscle performance of consumers without adequate scientific basis to support such claims.

January 2004

Consumer Advisory and Warning Letter: FDA Warns Consumers Not to Feed Infants "Better than Formula Ultra Infant Immune Booster 117"

On January 23, 2004, the Agency issued a warning to consumers that a product, Better Than Formula Ultra Infant Immune Booster 117, sold over the Internet as a dietary supplement should not be fed to infants. Even though NSP Research Nutrition labeled their product as a dietary supplement, FDA is concerned that the product appears to be represented as an infant formula in the product labeling.

On January 30, 2004, FDA issued a warning letter to the firm, advising the firm that it had not filed the necessary documentation for a new infant formula. The letter also advised the firm that the product was misbranded, in that it was labeled as a dietary supplement but did not meet the statutory requirements to be one.

December 2003

Judgment: Wildflower Pharmacal, Uttam Sethi

Wildflower Pharmacal (now Aulistic Vitamins Corp.) and Uttam Sethi were convicted of three felony counts relating to their manufacturing of dietary supplements that did not contain the labeled amounts of numerous nutrients. Judgment was filed in EDNY on 12/17/03. Mr. Sethi received 5 years probation, $ 3 million fine, and $1.5 million forfeiture. Wildflower Pharmacal received a $2.4 million fine.

Coral Calcium Consent Decree of Condemnation and Permanent Injunction

On December 17, 2003, the U.S. District Court for the Northern District of Illinois entered a Consent Decree of Condemnation and Permanent Injunction against Shop America. The decree prohibits "Shop America and each of its directors, officers, agents, representatives ... and any and all persons in active concert from directly or indirectly doing or causing any promoting, representing, or suggesting that an article manufactured, marketed, or distributed by Shop America, is safe or effective in the diagnosis or treatment of cancer, multiple sclerosis, lupus, heart disease, high blood pressure, or any other disease in man or other animals."

October 2003

Royal Tongan Limu

In October 2003, FDA witnessed the voluntary destruction of 90,000 bottles worth $2.7 million of Royal Tongan Limu, a liquid dietary supplement distributed by Dynamic Essentials, a subsidiary of NBTY, Inc. The firm was initially warned in a 2002 FDA "cyber letter" that website claims to treat various diseases such as cancer, arthritis, and Attention Deficit Disorder caused their products to be in violation of the law. Despite the warning, the product remained in distribution channels and, therefore, FDA recommended a seizure action. Dynamic Essentials ceased operation and no longer promotes or sells the products on its website.

Germanium Sesqioxide

In October 2003, FDA refused an entry of 20 kilograms of bulk germanium sesquioxide valued at $16,500, destined for use in human dietary supplements. Germanium has caused

nephrotoxicity (kidney injury) and death when used chronically by humans, even at recommended levels of use.

September 2003

Jean's Greens

In September 2003, at FDA's request, the U.S. Marshal seized herbal tea products known as Forticel and Forticel Mix from Jean's Greens in Norway, New York. The products claimed to treat and cure various life-threatening and serious illnesses such as cancer, thus causing the products to be unapproved drugs. FDA warned Jean's Greens in November 2001 to change its labeling for the products. The firm failed to comply. The value of the seized goods was more than $4000.

June 2003

SIGRA

In June 2003, FDA warned consumers not to purchase or consume SIGRA, STAMINA Rx and STAMINA Rx for Women, Y-Y, Spontane ES and Uroprin, manufactured by NVE Pharmaceuticals, Inc., in Newton, New Jersey, and distributed by Hi-Tech in Norcross, Georgia. These products, which were marketed as dietary supplements for sexual enhancement, were found to contain the prescription drug ingredient tadalafil, which can cause a drastic lowering of blood pressure when combined with prescription drugs containing nitrates. Tadalafil is the active ingredient in Cialis, an Eli Lilly product approved in Europe to treat male erectile dysfunction. Despite FDA's warnings, the defendant and his related businesses repeatedly sold dietary supplements that claimed to treat obesity and erectile dysfunction. Hi-Tech recalled the

products and in September 2003, a U.S. District Court Judge entered a Consent Decree of Permanent Injunction enjoining Hi-Tech Pharmaceuticals, National Urological Group, National Institute for Clinical Weight Loss, American Weight Loss Clinic, United Metabolic Research Center, and the President of these corporations, from distributing unapproved new drugs and misbranded drugs.

Global Source and Consulting, Inc.

In June 2003, a U.S. District Court entered a Consent Decree of Condemnation and Destruction for the seized products from Global Source and Consulting, Inc., which included 450 bottles and 57,000 bulk capsules of 20 products marketed as dietary supplement worth $19,000. Global Source agreed to destroy the products and to cease manufacture and marketing of "Vitamin Hut Scientific Cholesterol Support Program" or any similar red yeast rice product containing lovastatin, or any other drug product that is a new drug unless and until an approved new drug application is in effect for such product.

May 2003

Severe Acute Respiratory Syndrome (SARS)

In May 2003, FDA and FTC warned website operators, manufacturers and distributors to remove misleading or deceptive Internet claims that their products may prevent, treat or cure SARS. An Internet "surf"" conducted by FTC, FDA and the Ontario Consumer and Business Services, found numerous sites promoting a variety of SARS treatment or prevention products. The products include dietary supplements containing ingredients such as colloidal silver, ascorbic acid, beta glucan, pycnogenol, and oregano oil. FDA sent warning letters to 8 Internet firms

promoting dietary supplement products to treat or prevent SARS. FTC also notified violative firms that they were subject to possible civil or criminal actions under the FTC Act.

Gero-Vita International, Inc.

In May 2003, the FTC filed a complaint against Glenn Braswell and four of his corporations for making false and unsubstantiated claims that several products marketed as dietary supplements are "scientific breakthroughs" to treat or cure numerous serious medical conditions. FDA provided technical assistance and scientific support to FTC for this action. Products identified in the complaint were: Lung Support Formula, which claimed to cure or ameliorate asthma, emphysema, smoking damage and other respiratory problems; Antibetic Pancreas Tonic, which claimed to treat or cure diabetes and to lower blood sugar levels; and GH3 and GH3 Romanian Youth Formula, which claimed to extend life and prevent or treat Alzheimer's disease and other forms of dementia; Chitoplex to promote weight loss and reverse obesity without diet or exercise; and Testerex, which claimed to treat erectile dysfunction.

April 2003

Nature's Youth

In April 2003, FDA announced that Nature's Youth, LLC, of Centerville, Massachusetts, voluntarily destroyed approximately 5700 boxes of its product, "Nature's Youth hGH," worth $515,000. The action followed FDA's advisory that the products appeared to be misbranded by labeling that included unsubstantiated "structure/function" claims that the product would, among other things, "improve physical performance, speed recovery from training, increase cardiac output, and increase immune functions."

February 2003

Ancom Anti-Hypertensive

In February 2003, FDA investigators found that Ancom Anti-Hypertensive Compound tablets, which were marketed on the Internet and in retail stores as dietary supplements, contained several prescription drug ingredients, including reserpine, diazepam (Valium), promethazine, and hydrochlorothiazide. Best Life International, the manufacturer, ceased distribution and recalled the product. Subsequently in May 2003, Best Life International issued a voluntary recall and warned consumers not to buy or consume its product called Viga. Viga, marketed as a dietary supplement, was found to contain sildenafil, the active ingredient in Pfizer's Viagra. Sildenafil can cause life-threatening lowering of blood pressure when taken with nitrates.

January 2003

Yellow Jackets and Black Beauties

In January 2003, FDA and the U.S. Marshal's Service served an inspection warrant that would allow FDA to witness the voluntary destruction of $4 - 5 million worth of products known as "Yellow Jackets" and "Black Beauties." The warrant was served at NVE Pharmaceuticals, Inc., the manufacturer of the products, located in New Jersey. A distributor in the Netherlands promoted the products on the Internet as alternatives to street drugs. Yellow Jackets and Black Beauties are street terms for controlled substances and were sold as herbal street drug alternatives. In September 2002, FDA became aware of the tragic death of a 16-year old high school football player who had taken Yellow Jackets. FDA placed the products on Import Alert on October 7, 2002.

December 2002

EverCLR

On December 16, 2002, U.S. Marshals seized approximately 3,000 bottles of EverCLR, a dietary supplement, valued at more than $100,000. EverCLR was marketed by Halo Supply Company of San Diego, California, as a "natural" treatment for viruses such as the herpes virus and "cold and flu protection." None of these claims was substantiated. FDA charged that EverCLR was an unapproved and therefore, illegal, new drug because it was promoted to treat and prevent specific diseases. Because EverCLR's labeling lacked adequate directions for use, FDA also charged that the product was misbranded.

August 2002

Calm Focus

In August 2002, FDA issued a warning letter to Better Way Kids. This firm distributed "Calm Focus," a product promoted to treat Attention Deficit and Hyperactivity Disorder. Based on claims made for the treatment of disease, FDA charged that the product was an unapproved new drug. The firm corrected its product claims.

***U.S.* v. *Syntrax* Innovations, Inc., et. al**

U.S. v. *Syntrax Innovations, Inc.,* involved a substance called Triax, marketed by Syntrax as a dietary supplement for the treatment of obesity. FDA scientists determined that the product contained a potent thyroid hormone called tiratricol that, if taken in sufficient quantity, can cause heart attacks and strokes. FDA alleged that Triax could not be a dietary supplement because it was promoted to treat a disease (obesity) and because it did not contain any of the dietary

ingredients identified in DSHEA. In February 2001, the court entered an injunction barring the distribution of Triax.

***U.S.* v. *Lane Labs* USA, Inc. and Andrew Lane**

FDA brought an injunction action against Lane Labs USA, Inc., Andrew Lane, and three of Lane Labs' products, including its shark cartilage product, BeneFin. Lane Labs claimed that two of these products were dietary supplements, but the company promoted those products for the treatment of cancer and HIV (human immunodeficiency virus). The third product is a skin cream promoted for the treatment of skin cancer. FDA contended that the disease claims caused all three of these products to be unapproved, and therefore illegal, new drugs and misbranded drugs. The case is pending before the court for decision.

Mr. Chairman, thank you for this opportunity to testify. I am happy to answer your questions.

CFSAN/Office of Compliance
March 11, 2004

Androstenedione

Androstenedione Questions and Answers
Press Release: HHS Launches Crackdown On Products Containing Andro
White Paper: Health Effects of Androstenedione

Androstenedione Warning Letters

Androstenedione Warning Letters

Sample Androstenedione Warning Letter

List of Manufacturers Receiving Androstenedione Warning Letters

Firm Name/Location	Products
Advance Scientific Nutrition (PDF*) Hood River, Oregon	Androstene 100
AST Sports Science (PDF*) Golden, Colorado	Andro 100; Andro 250
Dymatize Nutrition (PDF*) Carrollton, Texas	Andro-100
Genetic Evolutionary Nutrition (PDF*) Marina Del Rey, California	Andro*GEN
German American Technologies (PDF*) Stamford, Connecticut	Stenandiol 2
Higher Power (PDF*) Boise, Idaho	Androstenedione 300; Androstenedione 100
ISS Research (PDF*) Charlotte, North Carolina	4-Androstene
Kaizen, Inc. (PDF*) Los Angeles, California	4-Dione
Lifelink (PDF*)	Androstenedione

Grover Beach, California	
MD Labs/Human Development Technologies (PDF*) Phoenix, Arizona	Andros-D
Mega-PRO International (PDF*) St. George, Utah	Androstenedione
Maximum Human Performance (PDF*) Cedar Grove, New Jersey	Endo-Stak
Olympian Labs (PDF*) Scottsdale, Arizona	Androstene Power
OSMO (PDF*) Palm Springs, California	Androstene 50; Androstene 100
Prolab Nutrition (PDF*) Chatsworth, California	Androstenedione
Schwartz Laboratories (PDF*) Cincinnati, Ohio	Andro Trybulen
Scientific Fitness (PDF*) Oakmont, Pennsylvania	Androstenedione
Sports One (PDF*) Wallingford, Connecticut	Andro-XS
Syntrax Innovations (PDF*) Cape Girardeau, Missouri Chaffee, Missouri	Libidione
TwinLab (PDF*) Hauppauge, New York	Andro Fuel
Ultimate Nutrition (PDF*) Farmington, Connecticut	Androstenedione
Universal Nutrition (PDF*) New Brunswick, New Jersey	AndroTech 100
Vitalabs (PDF*) Jonesboro, Georgia	V-4 Men

*PDF Readers are available for free from the Adobe Acrobat web site.

Androstenedione Questions and Answers
Press Release: HHS Launches Crackdown On Products Containing Andro
White Paper: Health Effects of Androstenedione

U.S. Food and Drug Administration
Department of Health and Human Services
CENTER FOR FOOD SAFETY AND APPLIED NUTRITION

CFSAN/Office of Compliance
March 11, 2004

Sample Warning Letter on Androstenedione

Androstenedione Warning Letters

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

[firm]
[address]

Dear Sir or Madam:

This letter concerns your product [product] that is labeled and/or promoted as a dietary supplement. The product labeling declares androstenedione (among other names, also called 4-androstenedione or 4-androstene-3,17-dione) as an ingredient.

The term "dietary supplement" is defined in 21 U.S.C. 321(ff) [section 201(ff) of the Federal Food, Drug, and Cosmetic Act (the Act)]. Given that you have labeled your product as a dietary supplement, we assume you have a basis to conclude that androstenedione is a "dietary ingredient" under 21 U.S.C. 321(ff)(1). Assuming that androstenedione is a "dietary ingredient," it would also be a "new dietary ingredient" for which a notification is required under 21 U.S.C. 350b(a)(2) and 21 CFR 190.6.

Under 21 U.S.C. 350b, a dietary supplement that contains a new dietary ingredient (i.e., a dietary ingredient not marketed in the United States before October 15, 1994) shall be deemed adulterated under 21 U.S.C. 342(f) unless it meets one of two requirements:

> (1) The dietary supplement contains only dietary ingredients that have been present in the food supply as an article used for food in a form in which the food has not been chemically altered; or
>
> (2) There is a history of use or other evidence of safety establishing that the dietary ingredient when used under the conditions recommended or suggested in the labeling of the dietary supplement will reasonably be expected to be safe and, at least 75 days before being introduced or delivered for introduction into interstate commerce, the manufacturer or distributor of the dietary ingredient or dietary supplement provides FDA with information, including any citation to published articles, which is the basis on which the manufacturer or distributor has concluded that a dietary supplement containing such dietary ingredient will reasonably be expected to be safe.

FDA is not aware of any information demonstrating that androstenedione was lawfully marketed as a dietary ingredient in the United States before October 15, 1994. Nor is FDA aware of any information demonstrating that this ingredient has been present in the food supply as an article used for food in a form in which the food has not been chemically altered. In the absence of such information, androstenedione is subject to the notification requirement for a new dietary ingredient in 21 U.S.C. 350b(a)(2) and 21 CFR 190.6. Because you have not submitted the required notification, your product is adulterated under 21 U.S.C. 342(f)(1)(B) and 350b(a).

Even if the required notification had been submitted, based on what we know now, we know of no evidence that would establish that your product is not adulterated. In the absence of a history of use or other evidence of safety establishing that androstenedione, when used under the conditions recommended or suggested in the labeling of your product, will reasonably be expected to be safe, a product containing androstenedione is adulterated under 21 U.S.C. 342(f)(1)(B) and 350b(a) as a dietary supplement that contains a new dietary ingredient for which there is inadequate information to provide reasonable assurance that such ingredient does not present a significant or unreasonable risk of illness or injury. Introduction of such a product into interstate commerce is prohibited under 21 U.S.C. 331(a) and (v). FDA is aware of no history of use or other evidence of safety establishing that androstenedione will reasonably be expected to be safe as a dietary ingredient. In the absence of such history of use or other evidence, your product would be considered adulterated.

We request that you take prompt action to correct these and any other violations associated with {product} and any other products marketed by your firm that contain the dietary ingredient androstenedione. We also remind you that the new dietary ingredient notification requirement applies to all dietary supplements that contain new dietary ingredients that have not been present in the food supply as articles used for food in a form in which the food has not been chemically altered.

Failure to immediately cease distribution of the product could result in enforcement action by FDA without further notice. The Act provides for seizure of violative products, injunction against the manufacturers and distributors of violative products, and criminal sanctions against persons responsible for causing violations of the Act.

We request that you advise us in writing, within 15 days of receipt of this letter, as to the specific steps that have been or will be taken to correct these violations, including any steps taken with respect to product currently in the marketplace, and an explanation of each step taken to assure that similar violations do not recur. Your reply should be directed to Jennifer Thomas, Compliance Officer, at the above address.

Sincerely,

Joseph R. Baca
Director
Office of Compliance
Center for Food Safety and Applied Nutrition

Time Line of Activities
To Establish Current Good Manufacturing
Practice Regulations (CGMPs) for Dietary Supplements

October 25, 1994 - DSHEA enacted, authorizing GMP regulations (section 402 (g)(2) of FD&C Act).

November 30, 1995 - FDA met with representatives of the dietary supplement industry to discuss the need for and potential structure of dietary supplement GMPs.

December 12, 1996 - advance notice of proposed rulemaking (ANPRM) sent to OMB.

February 6, 1997 - FDA issued ANPRM (62 FR 5700) asking for comments on whether to institute rulemaking to develop CGMP regulations for dietary ingredients and dietary supplements and what would constitute CGMP regulations for these products.

May 6, 1997 - FDA extended the comment period on the ANPRM until June 6, 1997 in response to several requests from interested persons.

February 1998 - FDA's Food Advisory Committee (FAC) established a Dietary Supplement Working Group to consider what constitutes adequate testing for identity of different dietary ingredients and what records are necessary to demonstrate that CGMPs are maintained throughout the manufacturing and distribution process.

Jan (approx.) 1999 - GMP Regulation determined to be an economically significant rule requiring a detailed economic impact statement under the Regulatory Flexibility Act of 1980, the Unfunded Mandate Reform Act of 1995, the Paperwork Reduction Act of 1995, and the Small Business Regulatory Enforcement Flexibility Act of 1996.

June 25, 1999 - The FAC working group presented its draft report during a public meeting of the FAC.

June 8 and July 20, 1999 - FDA held public strategic planning meetings to collect stakeholder comments on the development of our overall strategy for achieving effective regulation of dietary supplements. Development of CGMPs for dietary supplements was identified the as one activity that should be considered in an overall strategy.

July 12, September 28, and October 21, 1999 - FDA held public small business outreach meetings to collect information from industry and others that would help us to understand the economic impact on small businesses of CGMP regulations for dietary supplements.

Summer and fall of 1999 - FDA made eight site visits to dietary supplement manufacturing firms to gain first hand information on manufacturing processes for dietary supplements.

November 2, 2000 - FDA sent the draft proposed rule to the Office of Management and Budget (OMB) for review.

February 1, 2001 - As a result of the presidential transition, the draft proposed rule was withdrawn from OMB review.

March 28, 2001 - The proposed rule was resubmitted to OMB.

December 19, 2001 – Following discussions with OMB occurring over several months, FDA withdrew the proposal for revision.

October 4, 2002 - The revised proposal was sent to OMB.

January 16, 2003 - OMB cleared proposed rule for publication.

March 13, 2003 - FDA issued its 106 page proposed rule to establish CGMPs for dietary supplements (68 FR 12157 – 12263). Comments were initially due on June 11, 2003.

March 13, 2003 - FDA participated in a web cast and audio teleconference sponsored by the National Nutritional Foods Association (NNFA).

April 23, 2003 - FDA participated in an audio conference on GMP regulations sponsored by the Food and Drug Law Institute (FDLI).

April 29, 2003 and on May 6, 2003 - FDA held two public meetings to provide industry with an overview of the proposed regulations and to provide clarification on specific points in the proposed rule.

On May 4, 2003 - FDA representatives participated in an industry-sponsored forum on the GMP proposed rule in Secaucus, New Jersey.

May 9, 2003 - FDA held a satellite downlink broadcast to describe the proposed revisions and answer questions about the proposal. A meeting announcement was published on April 21, 3003 (68 FR19471).

May 19, 2003 - Based on requests from stakeholders, the comment period is extended an additional 60 days to August 11, 2003 (68 FR 27008).

August 11, 2003 to Present - Comment period is closed; FDA identifies and is addressing more than 400 significant comments in formulating the final rule.

U.S. Food and Drug Administration
Department of Health and Human Services
CENTER FOR FOOD SAFETY AND APPLIED NUTRITION

May 4, 2004

CFSAN 2004 Program Priorities

Letter from Center Director
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Dear Colleague, FDA Foods Community

I am pleased to share with you the FY 2004 Program Priorities for FDA's Center for Food Safety and Applied Nutrition (CFSAN). This document lays out the Center's work product expectations for the current fiscal year 2004 (October 1, 2003 through September 30, 2004), and is based on input we received from you (our stakeholders) as well as input generated internally, with focus on the question: ***"Where do we do the most good for consumers and the overall public health?"*** On behalf of CFSAN, I thank you for your input and your continuing interest in this process.

Our work plan is divided into four primary sections:

I. Assuring Food Safety and Security
II. Improving Nutrition and Dietary Supplement Safety
III. Assuring Food and Cosmetic Safety
IV. Assuring Food Safety: Crosscutting Areas

Last August, the Agency issued its Strategic Action Plan, Protecting and Advancing America's Health: Responding to new challenges and opportunities. CFSAN's work plan embraces the FDA Strategic Action Plan and our work plan incorporates action items to implement those goals and objectives.

Food Safety and security remains a central theme in the Administration's public health agenda. Our work plan is reflective of this continued focus. We will continue to concentrate on the issuance of final rules for the four major areas of the Bioterrorism Act of 2002 legislation and will continue our efforts to establish prevention measures or "shields" for commodities and food products identified as a high security concern.

This year's plan also reflects a commitment to revitalize and bolster our nutrition program. Helping consumers improve their nutrition is an increasingly urgent part of the FDA mission. Our efforts will focus on improving the health of the public by empowering people in the many choices they make every day that affect their health. We are working harder than ever to make sure the information consumers receive is scientifically valid and easily understood.

This is an ambitious and aggressive work plan. Our plan includes 168 "A-list" goals. These are listed in **bold-face** type in the document. Our goal is to complete at least 90 percent of these "A-List" items by the end of the current fiscal year, September 30, 2004. Activities on the "B-list" are those we plan to make significant progress on, but which we may not complete before the end of the fiscal year. Many of these are multi-year efforts that we anticipate placing on the "A-list" in subsequent years.

This work plan does not address our many ongoing regulatory, enforcement, research and communication activities as well as the myriad of unanticipated issues that also require a substantial investment of CFSAN resources (e.g., responses to outbreaks of foodborne illness). At mid-year, a progress review will be conducted and I will provide you with a mid-year progress report that will include any needed adjustments.

I cannot thank you, our stakeholders, enough for your continuing support. I believe that working together we can rise to the challenge of making sure Americans continue to enjoy a safe and healthy food supply.

Sincerely,

Robert E. Brackett, Ph.D.
Director
Center for Food Safety and Applied Nutrition

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DIETARY SUPPLEMENTS
A FRAMEWORK FOR EVALUATING SAFETY

Statement of

Alice M. Clark, Ph.D.
Vice Chancellor for Research and Sponsored Programs,
Frederick A.P. Barnard Distinguished Professor of Pharmacognosy
and
Research Professor of the Research Institute of Pharmaceutical Sciences
The University of Mississippi

and

Member, Committee on the Framework for Evaluating the Safety of Dietary Supplements
Food and Nutrition Board, Institute of Medicine
and Board on Life Sciences, National Research Council
The National Academies

before the

Subcommittee on Oversight of Government Management, the Federal Workforce and the
District of Columbia
Committee on Governmental Affairs
U.S. Senate

June 8, 2004

Good afternoon, Mr. Chairman and members of the Subcommittee. My name is Alice M. Clark. I am the Vice Chancellor for Research and Sponsored Programs of the University of Mississippi as well as a Frederick A.P. Barnard Distinguished Professor, Professor of Pharmacognosy, and Research Professor in the Research Institute of Pharmaceutical Sciences at the University. I also served as a member of the Committee on the Framework for Evaluating the Safety of Dietary Supplements of the Institute of Medicine and National Research Council.

The Institute of Medicine and the National Research Council are part of the National Academies, which also include the National Academy of Sciences and the National Academy of Engineering. The Institute of Medicine operates under the 1863 charter by Congress to the National Academy of Sciences to advise the government on matters of science, technology, and health. The National Research Council is the principal operating agency of both the National Academy of Sciences and the National Academy of Engineering in providing service to the government, the public, and the scientific and engineering communities.

I am here to talk about the report of the Committee on the Framework for Evaluating the Safety of Dietary Supplements. The report, *Dietary Supplements: A Framework for Evaluating* Safety, was released in April 2004. My comments will focus on the key findings and recommendations of the report.

The work of the committee was conducted under a contract initiated by the Food and Drug Administration (FDA). Over several decades, the agency tried several approaches to regulating supplements, sometimes meeting resistance from industry and the

public. In 1994 Congress passed the Dietary Supplement Health and Education Act, known as DSHEA, in order to define FDA's authority to regulate dietary supplements. DSHEA states that supplements are to "supplement the diet" and are thus to be regulated like foods, meaning that they are assumed to be safe. Therefore, like food processors, supplement manufacturers are not required to conduct specific and defined safety tests on their ingredients or to provide the FDA documentation on the safety of their products. Many of the supplements on the market are probably safe. However, to identify and take action on the occasional problem product, the FDA must rely on available evidence and information to evaluate whether the ingredient in question poses an unreasonable risk. To aid the FDA, the committee was asked to devise a science-based approach to evaluating the safety of supplement ingredients under the authority of current statutes.

Framework for Evaluating Safety

The committee's report offers the FDA a science-based approach by which the agency can use different kinds of available data to better identify supplements of concern, and then evaluate the safety of these ingredients. This approach works within the parameters of the current law governing how dietary supplements are regulated. This approach, called the framework, characterizes the nature of the scientific evidence that FDA is likely to encounter and describes a process for organizing that evidence to assess where a dietary supplement ingredient lies on a spectrum of concern.[1] As the level of concern rises, so does the potential for a "significant or unreasonable risk," the standard warranting regulation under the Food Drug and Cosmetic Act, as amended by DSHEA.

[1] The use of the term "concern" denotes a need for further investigation and inquiry by the FDA based on a relative level of interest arising from initial information.

The framework consists of three major components: signal detection, initial review of the signal, and integrative evaluation. The first component is signal detection and signals can come from many sources and originate from many types of scientific data. Given the significant number of dietary supplements the FDA's attention should focus on signals that indicate that a serious[2] health problem may result due to ingestion of a dietary supplement or ingredient. The second component of the framework is to conduct an initial review of available information. This allows the FDA to focus its efforts on the few dietary supplement ingredients that are strong candidates for regulation. The third step of the framework process is conducting an integrative evaluation of those dietary supplements that are deemed to warrant further investigation.

A key point of the report is that FDA does not have to find direct evidence of actual harm from use of a supplement ingredient to determine that the product poses an unreasonable risk to consumers' health. According to DSHEA, the agency can act to protect the public's health when an ingredient poses a significant or unreasonable risk. Determining whether an ingredient carries unreasonable risks does not require the same level of definitive proof that would be needed to document actual harm.

The report describes the different kinds of data the agency can use in its safety evaluation. Often, useful information on an ingredient's effects in people is lacking because the supplement manufacturers are not required to conduct pre-market testing or report evidence of adverse experiences. Moreover, historical use of an ingredient often is

[2] Serious—any experience resulting in any of the following outcomes: Death, a life-threatening adverse experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the individual and may require medical or surgical intervention to prevent one of the outcomes previously listed (in accordance with 21 C.F.R. 600.80 [2002] and 21 C.F.R. 314.80 [2002].

not sufficient to demonstrate that an ingredient does not cause harm. The report discusses the significance of the kinds of information available, such as data from animal studies, tests done in laboratories, or toxicity of similar or related substances. Some of these types of data may be sufficient by themselves for the FDA to determine that a supplement ingredient poses an unreasonable risk. The report classifies scientific information into four broad categories for use in determining the potential for serious harm for a specific dietary supplement ingredient—human data, animal data, related substances, and *in vitro* data. Guiding principles for evaluation of data to determine unreasonable risk are shown in Attachment 1 to this statement. They are also found in Box ES-1 of the report.

Key Recommendations

With the approach recommended in the report, it is possible for the FDA to conduct effective safety evaluations within the current regulatory framework established by DSHEA. However, in the process of developing the approach and reviewing the science, the committee noted that the constraints imposed by aspects of DSHEA limit the agency's ability to conduct these evaluations as effectively and efficiently as possible. Therefore, the report recommends some changes that could mitigate these constraints and make the law more effective in meeting the goal of protecting public health. For example, reports of adverse events associated with the use of a product can be an important way by which the FDA becomes aware of potential health risks. Currently, supplement manufacturers and distributors are not required to notify the agency about health problems that they discover related to the use of their products. The law should be modified to require such reporting. But other parties also bear responsibility for ensuring that health problems related to use are brought to the FDA's attention. Health professionals should be educated

about ways to report health concerns and encouraged to use them. Likewise, the toll-free number for the FDA's MedWatch should be printed on all supplements' packaging so that consumers have a clear way to relay any health concerns. More detail on these recommendations is in Attachment 2.

While the committee was not formed to do a cost analysis of implementing the framework, implementing any framework to systematically evaluate the safety of dietary supplement ingredients will require additional resources. Thus, the report recommends that Congress provide the FDA additional funding so that it can more effectively protect the public's health.

Barriers to Evaluating the Safety of Dietary Supplements

Through the process of developing the framework, the committee identified a number of legal and regulatory barriers to evaluating the safety of dietary supplements that hamper FDA's ability to protect the public health. The FDA currently has no authority to require the collection or reporting of specific safety data from dietary supplement manufacturers or distributors after their products are made available for sale to the public.

In line with these findings, members of the scientific and medical community have strongly advised that the regulatory mechanisms for monitoring the safety of dietary supplements, as currently defined by DHSEA, be revised. The constraints imposed on the FDA with regard to ensuring the absence of unreasonable risk associated with the use of dietary supplements make it difficult for the health of the American public to be adequately protected.

Thank you for the opportunity to address you on this important topic. I would be pleased to answer your questions.

Guiding Principles for Evaluating Data to Determine Unreasonable Risk

- General principles
  - Absence of evidence of risk does not indicate that there is no risk.
  - Proof of causality or proof of harm is not necessary to determine unreasonable or significant risk.
  - Integration of data across different categories of information and types of study design can enhance biological plausibility and identify consistencies, leading to conclusions regarding levels of concern for an adverse event that may be associated with use of a dietary supplement.
- Human data
  - A credible report or study finding of a serious adverse event in humans raises concern about the ingredient's safety and requires further information gathering and evaluation; final judgment, however, will require consideration of the totality of the evidence.
  - Historical use should not be used as *prima facie* evidence that the ingredient does not cause harm.
  - Considerable weight can be given to a lack of adverse events in large, high-quality, randomized clinical trials or epidemiological studies that are adequately powered and designed to detect adverse effects.
- Animal data
  - Even in the absence of information on adverse events in humans, evidence of harm from laboratory animal studies is often indicative of potential harm to humans.
- Related substances
  - Scientific evidence for risk can be obtained by considering if the plant constituents are compounds with established toxicity, are closely related in structure to compounds with established toxicity, or the plant source(s) of the botanical dietary supplement itself is a toxic plant or is taxonomically related to known toxic plant(s).
  - Supplement ingredients that are endogenous substances or may be related to endogenous substances should be evaluated to determine if their activities are likely to lead to serious effects. Considerations should include the substance's ability to raise the steady state concentration of biologically active metabolites in tissues and whether the effect of such increases would be linked to a serious health effect.
- *In vitro* data
  - Validated[1] *in vitro* studies can stand alone as independent indicators of risk to human health if a comparable exposure is attained in humans and the *in vitro* effects correlate with a specific adverse health effect in humans or animals.

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[1] In this report, *in vitro* assays are considered validated when their results have been proven to predict a specific effect in animals and/or humans with reasonable certainty (not necessarily universally accepted or without detractors).

Source: Box ES-3. IOM. 2004. *Dietary Supplements: A Framework for Evaluating Safety.* National Academies Press, Washington, DC. Prepublication copy.

Attachment 2

RECOMMENDATIONS

The following recommendations, while not part of the Framework itself, are designed to enhance the utility of the Framework and enhance the ability of the FDA to protect consumers from unreasonable risk of illness or injury resulting from use of dietary supplements.

- **Prospective systematic monitoring and tracking mechanism for dietary supplement ingredients should be maintained and refined.**

  A prospective, systematic method for recording and monitoring the history of safety issues with specific dietary supplements is necessary to implement the Framework for FDA to evaluate the safety of dietary supplement ingredients. During the period of this study, the FDA has developed a new method of monitoring and tracking dietary supplement adverse event reports. However, a prospective system is required that enables tracking of information leading to all levels of concern.

  The system should be open, transparent, and useful for establishing varying levels of concern related to dietary supplements as outlined in the Framework. Resources to support these activities should be provided to the FDA.

- **Adequate resources to protect the consumer under DSHEA must be provided.**

  While the committee did not conduct an analysis of the cost of implementing this Framework, implementation of any framework for comprehensive safety evaluation will generate an additional workload for the responsible staff at FDA. For the Framework to be effective, adequate resources must be available to FDA to collect and analyze available information.

- **Adverse Event Reporting:**
  - **DSHEA should be amended to require that a manufacturer and distributor report to the FDA, in a timely manner, any serious adverse event associated with use of its marketed product of which the manufacturer or distributor is aware.**
  - **The FDA should continue to work with the Poison Control Centers as a source of adverse event reports, and sufficient resources to support this activity should be provided.**
  - **The FDA should increase efforts to inform health care professionals and consumers that they should use the MedWatch adverse event reporting program to report adverse events associated with the use of dietary supplement ingredients.**
  - **The FDA MedWatch toll-free telephone number should be provided on product labels to facilitate reporting of adverse events.**

  Reports of adverse events are an important source of information by which the FDA becomes aware of potential risks to public health from exposure to dietary

supplement ingredients. It has been estimated that the FDA receives reports of less than one percent of all adverse events associated with dietary supplements. While spontaneous adverse event reports have recognized limitations, they have considerable strength as potential warning signals of problems requiring attention, making monitoring by the FDA crucial.

- **To initiate the 75-day premarketing review period, the distributor and manufacturer should be required to provide the FDA with all available data, both favorable and unfavorable, regarding the safety of the product.**

- **When the formulation or processing of a dietary supplement ingredient is changed, it should be considered a new dietary ingredient and subject to regulatory oversight as such.**

  Many dietary supplement ingredients on the market today have new formulations and are produced through very different processes than related dietary supplement ingredients in traditional usage, or even other dietary supplement ingredients bearing the same name. This may result in markedly different bioactive substances of potential harm, and very different kinetics (e.g., absorption, distribution in the body, metabolism, and excretion).

- **The FDA initiative to establish cGMPs for dietary supplement ingredients is supported and additional efforts to develop standards for content uniformity should be undertaken. Sufficient resources to support these efforts should be provided by Congress.**

  While the focus of this report is on developing a framework and not on safety issues related to good manufacturing practices, these are inseparable because variability in content hampers the evaluation of safety.

- **Adoption of the labeling changes recommended in *Inspector General Report: Dietary Supplement Labels: Key Elements* is urged.**

  Required labeling information that would be of use to the consumer in making informed decisions about safety is limited. Current regulations related to source of a product only require the name and place of business of the manufacturer, packer, or distributor to be on the label. There are usually few manufacturers of a product, but many distributors or packers. Thus both sources need to be on the label.

- **Additional Research on the Potential to Cause Harm:**
  - **The continued development of effective working relationships and partnerships between FDA and the National Institutes of Health is encouraged.**
  - **The FDA should ensure that its own National Center for Toxicological Research and the overall Department of Health and Human Services National Toxicology Program are optimally utilized when research is needed to further evaluate concerns.**

All federally supported research on dietary supplements conducted to assess efficacy should be required to include the collection and reporting of all data on the safety of the ingredient under study.

There is no legal or regulatory requirement that dietary supplement ingredient manufacturers conduct toxicology or safety pharmacology studies on their products or ingredients. Thus, experiments and studies to address safety issues will, in most cases, be initiated by the FDA or other federal agencies.

SOURCE: IOM 2004. *Dietary Supplements: A Framework for Evaluating Safety.* Washington, DC: National Academies Press. Prepublication Version. Pages ES-12 –ES-13.

STATEMENT

of the

American Medical Association

to the

Subcommittee on Oversight of Government Management,
the Federal Workforce and the District of Columbia
Committee on Governmental Affairs
United States Senate

Presented by Ronald M. Davis, MD
Member, AMA Board of Trustees

RE: DIETARY SUPPLEMENT ACT:
HOW IS FDA DOING 10 YEARS LATER?

June 8, 2004

Good afternoon Chairman Voinovich, Ranking Member Durbin, and members of the Subcommittee. My name is Ronald M. Davis, MD and I am a member of the Board of Trustees of the American Medical Association (AMA). I am a preventive medicine physician and serve as Director of the Center for Health Promotion and Disease Prevention at the Henry Ford Health System in Detroit, Michigan. I am pleased to be able to testify today on behalf of the AMA. The AMA commends the Subcommittee for its continued focus on the important issue of dietary supplements and their safety.

Introduction

The physician members of the AMA are very concerned about the quality, safety, and efficacy of dietary supplement products, especially herbal (botanical) products and supplements containing anabolic steroid-like ingredients and their precursors (i.e., substances that have the potential to be converted in the body into testosterone or other anabolic steroids). The AMA is particularly concerned about the rising tide of anabolic steroid abuse in adolescents, especially among girls. Many of these dietary supplements, including derivatives of potent veterinary products, are readily available over-the-counter or via the Internet. Yet, these products are largely unregulated under the Dietary Supplement Health and Education Act of 1994 (DSHEA). The AMA believes that DSHEA fails to provide for adequate regulatory oversight by the U.S. Food and Drug Administration (FDA) of dietary supplements and, as it has in the past, urges Congress to amend DSHEA so that dietary supplements are regulated the same way as are prescription and over-the-counter drugs.

Quality, Safety and Efficacy Concerns

Consumer interest in alternative therapies has greatly increased over the past several decades. Among the most commonly used alternative therapies are herbal remedies and megavitamins, which generally are classified as dietary supplements. It is estimated that in 2001, 70% of the U.S. population (152 million people) tried at least one dietary supplement. The use of herbal remedies has grown faster than any other alternative treatment method in the United States. The FDA has estimated that about 29,000 dietary supplements were on the market in 2001. Sales of dietary supplements in 2002 were over $18 billion.

The widespread availability and use of dietary supplements, and concerns by AMA members about the dangers of these products, raise some important questions that need to be addressed.

- Do these products actually contain the active ingredient(s) (and strength[s]) that their manufacturers claim on the labeling?
- Are these products really as safe as the promotional materials of the manufacturers claim them to be?
- Does the degree of safety change in individuals who have pre-existing diseases and conditions, or in those individuals who are also taking prescription medications?
- Are the structure/function claims for these products accurate and based on good science?
- Are these products being used inappropriately to treat diseases or potentially delaying individuals with diseases from obtaining effective prescription medications?

The AMA does not believe that satisfactory answers to these questions have been offered to either public health officials or the general public. Moreover, there are an increasing number of reports that the quality, safety and/or efficacy of some herbal remedies are unacceptable. Because dietary supplements are classified under DSHEA as foods rather than drugs, rigorous safety and efficacy standards are not required for these products. Also, standards for product quality and for Good Manufacturing Practices (GMP) do not yet exist.

Quality Issues

Under DSHEA, the name and quantity of each dietary ingredient in a dietary supplement must appear on the product's label. For proprietary blends, only the total quantity of all dietary ingredients in the blend must be stated. Currently, there are no standards for the purity and potency of many dietary supplement products nor are there finalized regulations for good manufacturing practices. Furthermore, manufacturers are not required to submit products to the FDA or to other standard-setting organizations, such as the United States Pharmacopeia (USP), for testing to ensure that the labeling accurately reflects the ingredients in the container.

Do dietary supplement products actually contain the active ingredient(s) and strength(s) that their manufacturers claim on the labeling? A number of studies published in the scientific literature suggest that this is not the case. These studies have shown wide variation in the content of the active ingredient(s) among dietary supplement products containing ginseng,

dehydroepiandrostenedione, St. John's wort, vitamin E, and saw palmetto. For example, in an analysis of 24 ginseng products, one-third had no active ingredient. There also have been documented reports of impurities (e.g., arsenic, lead, mercury, and pesticides) and adulterants (e.g., contamination with drugs, such as testosterone, alprazolam, warfarin and digitalis) in some dietary supplements, especially herbal products. The bottom line is that consumers cannot be sure that what is written on the product label is what is actually in the bottle.

Safety Issues

Are dietary supplement products really as safe as their manufacturers claim them to be? There is a growing body of published literature that suggests many dietary supplements are associated with adverse events and, in some cases, these adverse events can be severe in nature. Undoubtedly, ephedra has been the most discussed dietary supplement regarding safety problems. However, there are many other substances where safety concerns have been raised. For example, the FDA issued an urgent recall of all dietary supplement products containing aristolochic acid because it caused kidney failure. The FDA also advised manufacturers to remove all products containing the ingredient comfrey from the market because it is toxic to the liver. The FDA sent a letter to all health professionals seeking information about liver injury and products containing kava because of reports of liver toxicity associated with kava in Europe. However, because of the constraints that DSHEA imposes on the FDA, many of these products are still being marketed, according to the May 2004 issue of *Consumer Reports*.

In addition to causing side effects and toxicity, there also is a growing body of evidence that some dietary supplements, especially herbal remedies, can negatively affect health outcomes in patients with pre-existing conditions or in patients who are taking certain prescription drugs concurrently. For example, a literature review suggested that eight commonly used herbal remedies could result in a variety of complications in patients who are undergoing surgical procedures. There also are reports of adverse events resulting from concurrent administration of some herbal remedies with various prescription drugs. For example, St. John's wort induces enzymes that metabolize indinavir and can reduce the effectiveness of this HIV protease inhibitor to treat HIV infection. A study published in the September 17, 2003 issue of the *Journal of the American Medical Association* (JAMA) has convincing data that St. John's wort could reduce the efficacy of half the prescription drugs on the market. A number of potential and documented interactions between herbal remedies and warfarin, a drug that prevents blood clotting, also have been reported. Because patients often fail to inform their physicians about dietary supplements they are taking, and DSHEA does not require this information on labels, the potential for these interactions is very real and of significant concern.

Efficacy, Product Claims and Advertising

While there are published data to support the efficacy of some herbal remedies in the treatment of diseases (e.g., St. John's wort for mild-to-moderate depression and saw palmetto for benign prostatic hyperplasia), herbal remedies that are classified as dietary supplements cannot be labeled to treat diseases in the United States. Rather, dietary supplements only can

make so-called structure/function claims, i.e., a statement about the effect of a product on the structure or function of the body (e.g., help support healthy emotional balance). Unfortunately, published data to support structure/function claims is very limited. While the law requires that manufacturers be able to substantiate the truthfulness of structure/function claims, manufacturers are not required to provide this data to the FDA. Rather, the law only requires the manufacturer to include a disclaimer on the product label, "This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent disease."

Manufacturers of dietary supplements also may make health claims for their products if authorized by the FDA. Examples of a health claim are "calcium may reduce the risk of osteoporosis" and "diets low in sodium may reduce the risk of high blood pressure." However, when the FDA tried to impose the same high standard of scientific rigor to support a health claim for dietary supplements as is required for conventional foods, the dietary supplement industry sued the FDA and won. Thus, the FDA was forced to allow so-called "qualified" health claims, based on a lesser standard of scientific evidence, for dietary supplements.

Although DSHEA explicitly prohibits dietary supplement products from making disease claims, i.e., that the product diagnoses, mitigates, treats, or cures a specific disease, it appears that many vendors of dietary supplements are ignoring the law's prohibition in their promotion. In a 2003 article in JAMA, the authors analyzed over 400 Internet sites involved in the sale of herbal remedies. Over one-half of the sites made illegal disease claims for their products.

Ineffectiveness of DSHEA

The AMA believes that DSHEA fails to provide for adequate FDA regulatory oversight of dietary supplements and has supported changing the law for the past several years. The law is problematic for several reasons. First, it inappropriately classifies a whole variety of so-called "natural" substances as foods. Despite this classification, the reality is that herbal remedies, anabolic steroids or their precursors, and megadose vitamins are not foods. Rather, they are substances that have biological activity in the human body, including side effects, and are really "drugs." Thus, the AMA believes these substances should be regulated as drugs by the FDA.

The second problem with DSHEA is that the FDA's authority to regulate dietary supplements is insufficient to protect the health and welfare of the American public. According to a 2002 Harris poll, the majority of consumers believe that dietary supplements are safe and must be approved by a government agency such as the FDA before they can be sold to the public. However, since dietary supplements are not considered to be drugs, they are exempt from the expert scientific evaluation that has helped ensure the safety and effectiveness of drugs. Under the provisions of DSHEA, dietary supplement manufacturers, unlike drug manufacturers, are not required to provide evidence of efficacy or safety prior to marketing their products. Moreover, except for a supplement that contains a "new dietary ingredient" (i.e., one not marketed in the United States prior to passage of DSHEA in 1994), dietary

supplements are not required to have FDA approval or to be registered with the FDA before they are produced and marketed. Thus, the benefit/risk ratio for dietary supplements is far less certain than it is for drugs, and it is very difficult to substantiate the claims for these products.

As previously discussed, dietary supplements, including herbal remedies, cannot make disease claims. However, distinguishing between a disease claim and a structure/function claim may be difficult. The AMA believes that some structure/function claims (e.g., "inhibits platelet aggregation") could easily be construed as disease claims by a consumer (e.g., "prevents heart attacks"). This could lead a consumer to inappropriately treat a disease with an herbal remedy. For example, the structure/function claim, "improves absentmindedness" could be misinterpreted as a treatment for Alzheimer's disease. Similarly, individuals infected with the human immunodeficiency virus (HIV) may believe that an herbal remedy that claims to "support the immune system" is a therapy for their disease.

Of significant concern to the AMA is that DSHEA does not require manufacturers of dietary supplements to report newly identified safety problems associated with their marketed products to the FDA. As a result, the FDA relies mostly on its voluntary adverse event reporting system to identify safety problems. However, the Office of Inspector General of the Department of Health and Human Services concluded in a 2001 report that FDA's adverse event reporting system detects relatively few adverse events, that FDA lacks critical information to adequately assess signals of possible public health concerns generated by adverse event reports (AERs), and that, as a result, FDA rarely takes safety actions related to the adverse event reporting system. (*"Adverse Event Reporting for Dietary Supplements: An Inadequate Safety Valve," OEI-01-00-00180*). The AMA agrees with the OIG's recommendations that included requiring dietary supplement manufacturers to report adverse events to the FDA and encouraging physicians, other health professionals, and consumers to voluntarily report potential adverse events to the FDA. More recently, the Institute of Medicine, in their report "*Dietary Supplements: A Framework for Evaluating Safety*" (2004) affirmed the OIG's recommendation that DSHEA should be amended to require manufacturers of dietary supplements to report serious adverse events to the FDA.

In addition to the problems with relying upon voluntary AERs, under DSHEA once a dietary supplement is marketed the burden falls entirely upon the FDA to demonstrate that a dietary supplement presents a "significant or unreasonable risk of illness or injury." Only then can the FDA take regulatory action against the dietary supplement. This has proven to be a high hurdle for the FDA to clear. Ephedra is perhaps the best example of how difficult it is under DSHEA to regulate unsafe dietary supplements. The AMA had asked the FDA for several years to remove ephedra-containing dietary supplements from the United States market. Yet, even for a substance as dangerous as ephedra, it took the FDA seven years to ban the product. While the AMA is very pleased that the FDA did ban ephedra earlier this year, we are concerned that it took so long to take action against this dangerous product. We believe that a major reason for this delay is the constraints that DSHEA imposes on FDA's regulatory authority.

Recommendations

Because of the problems discussed above, the AMA strongly urges Congress to amend DSHEA to require dietary supplements to be regulated similar to drugs. Specifically, the AMA recommends that:

1. Dietary supplements, including those products already in the marketplace, be reviewed and undergo FDA pre-market approval for evidence of safety and efficacy;
2. Dietary supplements meet standards established by the United States Pharmacopeia for identity, strength, quality, purity, packaging and labeling;
3. Dietary supplement manufacturers comply with FDA post-marketing requirements to report adverse events, including drug interactions; and
4. Dietary supplements that are anabolic steroids or precursors to anabolic steroids be reclassified as prescription drugs subject to the Controlled Substances Act.

The AMA supports pending legislation, such as S. 722 (the "Dietary Supplement Safety Act"), sponsored by Senator Durbin, and S. 2195/H.R. 3866 (the "Anabolic Steroid Control Act of 2004"), that would make some of the above changes.

In the absence of modifications to the current federal law, the FDA must aggressively regulate dietary supplements to the fullest extent possible to fulfill its obligation to protect the health of the American public. The AMA has expressed this view to the FDA on numerous occasions through letters to the Commissioner and to various FDA Dockets.

The AMA has recommended that the FDA focus on three broad areas: 1) FDA must ensure that consumers readily understand the differences between drug products and dietary supplement products (particularly herbal remedies) so each type of product is used appropriately; 2) FDA must ensure that dietary supplements, including herbal remedies, are of high quality and have a safety profile that warrants direct purchase by consumers without health professional supervision; and 3) to the extent possible under current law, FDA must ensure that structure/function claims for dietary supplements, including herbal remedies, can be substantiated by good science.

The AMA has recommended that the FDA develop an extensive educational campaign to inform consumers about the differences between drug products and dietary supplement products, including herbal remedies. It is imperative that consumers have the necessary knowledge to understand the limitations of dietary supplement products and when they should contact a physician to be appropriately diagnosed and treated with drugs that have known effectiveness for the treatment of diseases, disorders, and conditions. The AMA encourages physicians to ask their patients about any medications and other substances they are taking. Consumers must understand the importance of informing their physicians about the dietary supplements that they are taking so that the physician can discuss any known or potential problems that could occur between the dietary supplement and a pre-existing disease or between the dietary supplement and any prescribed medication(s).

The lack of adequate information on the efficacy, adverse reactions, and interactions of dietary supplements hinders informed decision-making by consumers. Thus, in comment letters, the AMA has urged the FDA, to the extent possible, to require manufacturers of dietary supplement products to include important risk information (e.g., contraindications) on product labels. Also, the AMA has recommended a broader disclaimer on the labels of all dietary supplement products, as follows: *"This product has not been evaluated by the Food and Drug Administration and is not intended to diagnose, mitigate, treat, cure, or prevent disease. This product may have significant adverse side effects and/or interactions with medications and other dietary supplements; therefore, it is important that you inform your doctor that you are using this product."*

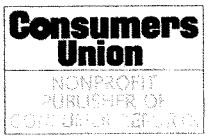
The AMA also has encouraged the FDA to do its utmost to prevent the use of structure/function claims that can blur the distinction between a drug and a dietary supplement. The AMA has opposed allowing dietary supplements to make implied disease claims or claims for abnormal conditions associated with natural states. Failure to adequately distinguish structure/function claims (for dietary supplements) from disease claims (for drugs) will increase confusion among consumers regarding appropriate therapies, and diminish the FDA's ability to protect the health of the public.

Dietary supplement products will be used primarily by healthy individuals without health professional supervision, and it is imperative that the risks of these products are minimal for this population. Thus, the FDA must ensure that dietary supplement products actually contain the ingredient(s) (and strength[s]) that the manufacturers claim on the labeling, and that these products are manufactured using Good Manufacturing Practices (GMP). Furthermore, the FDA must carefully monitor the safety profiles of marketed dietary supplements to ensure the American public that these products carry minimal risk. The FDA must take swift action to remove from the market those dietary supplement products that present unnecessary risk to consumers.

The AMA believes that the FDA should rely upon the USP to set standards for the identity, strength, quality, purity, packaging, and labeling of all dietary supplements, including herbal remedies. Furthermore, the FDA should require, or if that is not possible, strongly recommend that all dietary supplement products meet USP standards. Such products should be allowed to carry a statement that the product meets the USP's standards. Dietary supplement products that fail to meet USP standards preferably should be removed from the market or, if that is not legally possible, consumers should be strongly discouraged from using these products.

Conclusion

In conclusion, the AMA appreciates the opportunity to testify on this critical public health issue, and looks forward to working with Congress to make the necessary changes to DSHEA to provide for more appropriate regulation of dietary supplements by the FDA in order to protect the health of our nation's consumers.



TESTIMONY OF

CHARLES W.F. BELL, PROGRAMS DIRECTOR
CONSUMERS UNION OF U.S., INC.

ON

"DIETARY SUPPLEMENTS SAFETY ACT:
HOW IS FDA DOING 10 YEARS LATER?"

BEFORE THE

SENATE COMMITTEE ON GOVERNMENTAL AFFAIRS,
SUBCOMMITTEE ON OVERSIGHT OF GOVERNMENT MANAGEMENT, THE FEDERAL
WORKFORCE AND THE DISTRICT OF COLUMBIA

June 8, 2004

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Good morning, Chairman Voinovich, Ranking Member Durbin, and other members of the Committee. Thank you for providing me the opportunity to come before you today. I am Charles Bell, Programs Director for Consumers Union.[1] Consumers Union is the nonprofit publisher of *Consumer Reports* magazine. Since 1936, our mission at Consumers Union has been to test products, inform the public, and protect consumers. Today I offer this testimony on dietary supplements as part of our consumer protection function.

The Dietary Supplement Health and Education Act of 1994 (DSHEA) created a very serious regulatory loophole that has opened the floodgates to thousands of untested dietary supplement products. While many dietary supplements, including most vitamins and minerals taken within recommended limits, are generally safe and can have important health benefits for consumers, there is a significant and growing number of highly questionable products that would probably not be allowed on the market if they were subject to pre-market safety testing.

Under DSHEA, the burden of proof for removing unsafe products has been inappropriately shifted from manufacturers to government. As former FDA director David Kessler has stated, "Congress put the FDA in the position of being able to act only after the fact and after substantial harm has already occurred."

In the aftermath of DSHEA, unsafe dietary supplement products can remain on the market for many years, in the same stream of commerce as products approved by the FDA as safe and effective for their intended use. Further, new dietary supplement products can be introduced overnight that contain novel, untested ingredients and/or novel combinations of new and/or existing supplement ingredients. Health providers and public health authorities typically receive little pre-market or post-market information about how such products may affect human health, and interact with medicines that patients are already taking.

Even where serious safety problems are documented, it is difficult for the FDA to take prompt action to protect consumers. Unless the FDA meets a high standard of proof that a dietary supplement creates "a significant or unreasonable risk," it cannot ban it. Over the last 10 years, the FDA has typically relied on warnings and voluntary compliance to address supplement hazards, allowing many dangerous products to remain on the market.

UNSAFE SUPPLEMENTS CAN REMAIN ON THE MARKET FOR MANY YEARS

In 1995, *Consumer Reports* magazine published a list of five supplements that according to the FDA can cause serious harm to consumers--ephedra, chaparral, comfrey, lobelia, and yohimbe.

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[1] Consumers Union is a nonprofit membership organization chartered in 1936 under the laws of the State of New York to provide consumers with information, education and counsel about goods, services, health, and personal finance; and to initiate and cooperate with individual and group efforts to maintain and enhance the quality of life for consumers. Consumers Union's income is solely derived from the sale of *Consumer Reports*, its other publications and from noncommercial contributions, grants and fees. In addition to reports on Consumers Union's own product testing, *Consumer Reports* and *Consumer Reports Online* (with approximately 5 million paid circulation) regularly carry articles on health, product safety, marketplace economics and legislative, judicial and regulatory actions which affect consumer welfare. Consumers Union's publications carry no advertising and receive no commercial support.

Nine years later, ephedra was finally removed from the marketplace on April 12, 2004, many years after the FDA first received reports of serious consumer health problems, including deaths and disabling injuries. The other four supplements are still being marketed and sold in retail stores and on the Internet.

In May 2004, *Consumer Reports* published a new list of 12 hazardous dietary supplements, including the four herbs named in the 1995 report, that are too dangerous to be on the market according to government warnings, adverse-event reports, and medical experts.

These "dirty dozen" unsafe supplements, which *CR* easily purchased in stores and online in February, include:

- **Aristolochia:** An herb conclusively linked to kidney failure and cancer.
- **Yohimbe:** A sexual stimulant linked to heart and respiratory problems.
- **Chaparral, comfrey, germander, and kava:** All known or likely causes of liver failure.
- **Bitter orange:** Its ingredients have effects similar to the banned weight-loss supplement ephedra.

The potentially dangerous effects of most of these products have been known for more than a decade, and at least five of them are banned in Asia, Europe, or Canada.

The *Consumer Reports* article describes the case of Beverly Hames, who went to an acupuncturist in 1992 seeking a "safe, natural" treatment for an aching back. She obtained a selection of Chinese herbal products, at least five of which were later found to contain aristolochic acid. By mid-1994, she had symptoms of kidney failure, and in 1996 she underwent a kidney transplant. She must take anti-rejection drugs for life. The herbs' distributor said his Chinese suppliers had substituted Aristolochia for another herb without his knowledge.

"I was told that these herbs are safe, they're natural and they've been used for hundreds of years," Hames said. "I went from a perfectly healthy person to kidney failure in a very short period of time."

In addition to being a powerful kidney toxin, Aristolochia is on the World Health Organization's list of human carcinogens. The herb has been banned in seven European countries, Egypt, Japan and Venezuela. In the U.S., the FDA issued a warning to consumers and industry and an import alert in April 2001. And most recently on May 19th, DHHS's National Toxicology Program nominated Aristolochia for review for possible listing in the upcoming 12th edition of the governments' Report on Carcinogens.[2]

While we believe that all of the 12 supplements named in our report should be removed from the marketplace immediately, we believe it would be a serious mistake to attempt to address the crisis in supplement safety only on an ad-hoc, substance-by-substance basis. We believe that the consumer interest also requires establishment of an effective preventive safety system that would include pre-market safety evaluation, mandatory reporting for adverse events, and increased FDA regulatory authority to take prompt action against known and emerging hazards.

[2] Federal Register, 5/19/04, p. 28940

HOW MANY OTHER HAZARDOUS SUPPLEMENTS ARE THERE?

In addition to the 12 priority supplements named in our article, we think it is likely that there are other dietary supplement products that pose unacceptable risks to consumers.

To take just three other examples:

- Long-term use of dietary supplements containing colloidal silver can lead to agyria, a condition that turns skin gray and/or blue. According to several experts and respected sources, in recent years, silver-containing products have been marketed with unsubstantiated claims that they are effective against AIDS, cancer, and many other diseases and conditions.[3]
- Usnic acid, a supplement ingredient derived from lichens, may be highly toxic to the liver, and has been linked to reports of liver failure. The FDA has issued warnings about products containing usnic acid, and is investigating whether to take further action.[4]
- Ginkgo biloba, a popular supplement taken to enhance memory taken by as many as 11 million Americans, may reduce platelets in the blood, and make it more difficult for the blood to clot. This can cause excessive bleeding, and in some cases strokes. Because of the potential complications with surgical procedures, Dr. John Neeld, the president of the American Society of Anesthesiologists, advises consumers to discontinue the use of herbal medicine at least 2 to 3 weeks prior to surgery.[5]

Given that there are currently 30,000 dietary supplement products on the market, and 1,000 new products entering the market each year, it is important for Congress and the FDA to take a broad view of supplement safety. While most supplements are probably safe, consumers face particular risks from certain herbs that are highly toxic, and supplements that contain untested steroid equivalents. Without additional resources and regulatory authority, it simply is not possible for the FDA or anyone to know exactly how many more of these products pose serious hazards to consumers. The fact that we don't know the full extent of the supplement dangers ought to be serious cause for alarm.

EPHEDRA SUPPLEMENTS FINALLY REMOVED FROM MARKET IN APRIL 2004

Like many consumer and public health organizations, we were very pleased that the FDA finally took action to remove dietary supplements containing ephedra from the marketplace in January 2004. However, we are very concerned that the FDA's action came too late for many consumers, who experienced unacceptable health damage, including strokes, seizures, heart

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[3] For example, see "Rosemary's Story," by Rosemary Jacobs, available on the Web at: http://homepages.together.net/~rjstan/rose2.html

[4] Grady, Denise. "Seeking to Fight Fat, She Lost Her Liver," The New York Times, March 4, 2003, p.1. "After ephedra ban, FDA is checking other supplements, says Crawford," Nutraceuticals International, Vol 9., No. 5, May 2004.

[5] American Society of Anesthesiologists, "Anesthesiologists Warn: If You're Taking Herbal Products, Tell Your Doctor Before Surgery," posted on the Web at http://www.asahq.org/patientEducation/herbal.htm

attacks and deaths. Despite numerous serious warning signals, the agency failed to take action in a timely way to remove the product from the marketplace.

By the time the FDA finally moved to ban ephedra sales, ephedra was already being driven out of the marketplace by high profile deaths of athletes, the resulting negative media attention, litigation, rising insurance costs, and statewide bans in three states (Illinois, New York and California). Professional sporting organizations had taken action to prevent use of ephedra by athletes. The U.S. Army and Air Force military exchanges had moved to remove dietary supplements containing ephedra from military commissary shelves worldwide.

Ephedra is a poster child for a failed policy. We need to examine what went wrong in this instance, because new dietary supplements that contain existing or novel ingredients, and reformulations or new combinations of those ingredients, are being constantly introduced, at a rate of 1,000 new supplement products per year. We need to understand why the signals of an urgent public health problem failed to trigger prompt action by the federal government.

Consumer groups and medical providers had been urging the federal government to take action against ephedra literally for years. Consumers Union worked very hard to get the states of Illinois, New York and California to ban ephedra at the state level, which they did successfully, months before the FDA finally took action. We did this because consumers were at risk and in real danger. State legislators could see this was an important community issue, that the federal government was failing to address.

As long ago as September 1994, the FDA had reported that it was receiving consumer complaints about health effects associated with the use of ephedra.[6] From January 1993 through October 2000, the FDA received 1,398 reports of adverse events linked to herbal supplements containing ephedra, including 81 deaths, 32 heart attacks, 62 reports of cardiac arrhythmia, 91 reports of hypertension, 69 strokes and 70 seizures. By June 2003, the GAO reported the FDA had received a total of 2,277 adverse event reports about ephedra.

These reports are likely just the tip of the iceberg. The vast majority of adverse reactions to dietary supplements or medications are never reported to the FDA, or indeed to any health professional or agency. A study commissioned by the FDA estimated that the adverse event reports the FDA receives represent less than 1 percent of all the adverse events associated with dietary supplements.[7]

POST-MARKETING SURVEILLANCE OF DIETARY SUPPLEMENTS IS "AN INADEQUATE SAFETY VALVE"

In April 2001, the Office of Inspector General at the Department of Health and Human Services concluded that the FDA's adverse event reporting system was "an inadequate safety valve"

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[6] "Adverse Events with Ephedra and Other Botanical Dietary Supplements," FDA Medical Bulletin, September 1994, posted on the Web at: http://vm.cfsan.fda.gov/~dms/ds-ephe2.html

[7] Walker, A. "The Relation Between Voluntary Notification and Material Risk in Dietary Supplement Safety," FDA Commissioned Paper, March 9, 2000.

because of inadequate authority and organizational capacity to collect and take action on adverse event reports.[8] The report noted that in contrast to requirements for monograph drugs and new drug application (NDA) drugs, manufacturers of dietary supplements are not required to register their companies or their products with the FDA. As a result, the FDA does not have a list of supplement products and ingredients when it receives an adverse event report. The Inspector General found that FDA was unable to determine the ingredients for 32 percent of products mentioned in adverse event reports (AERs). It also lacked product labels for 77 percent of the products mentioned in the AERs, and product samples for 69 percent of products that it requested. For products referenced in the AERs, the FDA was unable to determine the manufacturer for 32 percent of the products, and the city and state for 71 percent of manufacturers.[9]

POISON CONTROL CENTERS RECEIVED MANY REPORTS REGARDING ADVERSE REACTIONS TO SUPPLEMENTS CONTAINING EPHEDRA

However, in addition to the direct reports that the FDA receives, there were other important signals of problems with dietary supplements containing ephedra. According to the American Association of Poison Control Centers, accidental or intentional incidents involving ephedra have resulted in thousands of consumers visiting emergency rooms and health care facilities for treatment.

In its most recent annual report, the AAPCC indicates that in the year 2002 alone there were:

- 1,556 reported events relating to exposure to dietary supplements containing ephedra as a sole ingredient, including one death, 248 adverse reactions, 20 "major effects" (defined as exhibiting signs or symptoms that were life-threatening or resulted in significant residual disability) and 274 "moderate effects" (defined as exhibiting symptoms or signs that were more pronounced, more prolonged or more systemic in nature than minor symptoms--and where usually some form of treatment is indicated). Of the 1,556 exposures, 843 persons (54%) were treated in a health care facility.

- 8,770 reported events linked to exposures to multi-botanical supplements containing ephedra as an ingredient, including two deaths, 1,180 adverse reactions, 88 "major effects" and 1,531 "moderate effects." Of the 8,770 exposures, 4,827 persons (55%) were treated in a health care facility.[10]

For herbal and homeopathic dietary supplements as a whole, the AAPCC estimates that there were nearly 22,928 reported exposure events in the year 2002. Of this total, 8,831 people were treated in health care facilities.

MANUFACTURERS HAVE SUPPRESSED INFORMATION REGARDING DIETARY SUPPLEMENT ADVERSE EVENTS

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[8] Office of Inspector General, Department of Health and Human Services, "Adverse Event Reporting For Dietary Supplements: An Inadequate Safety Valve," April 2001, OEI-01-00-00180.
[9] Ibid, p. ii.
[10] Watson, et al, "2002 Report of the American Association of Poison Control Centers Toxic Exposure Surveillance System," American Journal of Emergency Medicine, Vol. 21, No. 5, September 2003, p. 351-421.

A second very important source of data on problems with ephedra were adverse event reports received by manufacturers. Strong evidence has now emerged that manufacturers of ephedra supplements concealed substantial numbers of consumer complaints regarding their products:

- On August 15, 2002, the Justice Department disclosed that it was investigating whether Metabolife, a major manufacturer and distributor of ephedra products, had made false statements to the FDA regarding the existence of consumer complaints about its products. On the same day, Metabolife announced that it would turn over 13,000 consumer health complaints or "adverse event reports" to the FDA.[11] After analyzing the Metabolife adverse events reports, the special investigations division of the House Committee on Government Reform concluded that 2,000 of the 13,000 reports were "significant" effects, including three deaths, 20 heart attacks, 24 strokes, 40 seizures, 465 episodes of chest pains and 966 reports of heart rhythm disturbances.[12]

- Two years ago, depositions in a lawsuit in San Francisco against E'ola (a Utah-based multilevel-marketing firm) regarding a death allegedly linked to ephedra revealed that the company had received 3,500 customer complaints about one of its ephedra weight-loss products. According to the San Francisco Chronicle, none of the complaints were ever disclosed to the FDA.[13]

While it isn't clear how many other manufacturers and sellers of other dietary supplement products may be suppressing information regarding potential health effects, those examples do not inspire confidence that serious health impacts arising from the use of herbal supplements will be promptly reported to responsible health authorities under a voluntary reporting system. This also underscores the dangers of allowing herbal medicines in the marketplace without premarket safety testing and a rigorous post-marketing surveillance system.

In the five years after DSHEA took effect, from 1994 to 1999, fewer than 10 of the more than 2,500 reports that the FDA received came from manufacturers, according to a 2001 estimate from the inspector general of the U.S. Department of Health and Human Services.

THE FDA'S INABILITY TO COLLECT AND ACT ON MOUNTING ADVERSE EVENT REPORTS CREATED A SERIOUS GAP IN CONSUMER PROTECTION

When we add this all up, the federal government's failure to promptly act on available signals of serious consumer health problems with a particular dietary supplement is very disturbing. Consumers expect government to take an active role in ensuring that dietary supplements are safe and effective.

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[11] Neergaard, L. Feds investigate top ephedra seller, Associated Press, August 15, 2002.
[12] Crabtree, P. Metabolife understated danger: firm glossed over complaints about herb ephedra, panel told. San Diego Union Tribune, October 9, 2002.
[13] Howe, K. FDA Stops Tracking Herbal Remedies: Agency says it doesn't have the funding to assess adverse reactions, San Francisco Chronicle, February 14, 2000, p. A1.

Over the years, consumers have come to rely on the FDA to ensure that products that appear on the shelves in their local retail store or pharmacy have been tested and are safe for their use. By exempting dietary supplements from most types of oversight required for prescription and over-the-counter drugs, DSHEA has created a troubling and unexpected gap in consumer protection.

Many consumers are surprised to learn the government does not currently evaluate the safety of dietary supplements before they are sold.[14] This situation poses a serious risk to public health, and amounts to a vast, uncontrolled clinical trial on an unsuspecting public. Mr. Joseph Levitt, Esq., Director of the FDA's Center for Food Safety and Applied Nutrition, testified in Congress in March 2001 that the current "regulation of dietary supplements is, for the most part, a post-marketing program."[15]

As noted above, dietary supplement products are sold in the same stream of commerce as approved over-the-counter products, and consumers often assume that if they were not safe, the government would not permit them to be sold.

In an October 2002 nationwide Harris Poll of 1,010 adults, 59 percent of respondents said they believed that supplements must be approved by a government agency before they can be sold to the public. Sixty-eight percent said the government requires warning labels on supplements' potential side effects or dangers. Fifty-five percent said supplement manufacturers can't make safety claims without solid scientific support.

Unfortunately, the respondents in the poll were incorrect. None of those widely expected protections exist for dietary supplements—they exist only for prescription and over-the-counter medicines. With respect to testing for hazards, before approval, drugs must be proved effective, with an acceptable safety profile, by means of lab research and rigorous human clinical trials involving a minimum of several thousand people, and several years. In contrast, supplement manufacturers can introduce new products without any testing for safety and efficacy. The maker's only obligation is to send the FDA a copy of the language on the label.

Drug labels and package inserts must mention all possible adverse effects and interactions. But supplement makers do not have to put safety warnings on the labels, even for products with known serious hazards. With respect to post-surveillance monitoring, drug companies are required by law to tell the FDA about any reports of product-related adverse events that they receive from any source. Almost every year, drugs are removed from the market based on safety risks that first surfaced in those reports. But as we have just seen, supplement makers are not required by law to report adverse events. The reporting system is strictly voluntary, and apparently yields very few reports to the FDA.

We wonder, as we sit here today, what else manufacturers may have known about the dangers of ephedra and other dietary supplements, including those on our "dirty dozen" list. Unless the

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[14] For example, see "Widespread Ignorance of Regulation and Labeling of Vitamins, Minerals and Food Supplements," *Health Care News*, Harris Interactive, December, 2002; and Blendon, R. et al., "Americans' Views on the Use and Regulation of Dietary Supplements," Arch. Intern. Med., Vol 161, March 26, 2001, p. 805-810.
[15] Statement by Joseph Levitt, Esq., Director, CFSAN/FDA, before the Committee on Government Reform, March 20, 2001, available on the Web at http://www.fda.gov/ola/2001/dietary.html

Congress acts to tighten requirements for adverse event reporting by manufacturers, FDA will continue to lack vital information that is needed to ensure the safety of dietary supplements.

CONSUMERS WANT ADDITIONAL PROTECTIONS TO ENSURE SUPPLEMENTS ARE SAFE

Last month, Consumers Union conducted an online survey of a random sample of 1,221 adults regarding dietary supplements, as part of a regular national consumer issue survey that we perform. We read respondents a short factual statement about the recent ephedra ban, *Consumer Reports*' findings regarding dangerous supplements, and gaps in dietary supplement regulation. We then asked whether they agreed or disagreed with five statements. The survey found that:

- More than 8 in 10 respondents agree that poor regulation of supplements posed a personal risk to themselves and their families.
- More than 9 in 10 want the sale of supplements to be conditioned on safety and efficacy.
- Virtually everyone (96%) agreed that supplement producers should be required to report adverse events, as is required for prescription drugs.
- Similarly, 96% want product risk information to be included on dietary supplement labels.
- Fewer than 1 in 5 respondents feel that supplements already are sufficiently regulated.

Concern about dietary supplements was broader than for any other consumer issue in our multi-issue survey, which also included questions about car safety, cable television, fuel efficiency, and cell phones.[16]

We believe very strongly that the current serious gaps in consumer protection in DSHEA are not in the interest of dietary supplement consumers. Consumers turn to dietary supplements because they think these products will promote health and wellness. It is very important to ensure that these products are safe and do not themselves create serious health problems. Consumers who take supplements should not be test animals for highly questionable products that have not been sufficiently tested by their manufacturers prior to coming to market.

DIETARY SUPPLEMENTS MARKETED AS "EPHEDRA-FREE" ARE NOT NECESSARILY SAFE

Many companies are currently rushing to market with new weight-loss supplements that are being marketed as "ephedra-free," which many consumers may assume are safe for consumer use. But as Dr. Paul Coates of the National Institute of Health's Office of Dietary Supplements has warned, "The fact that a dietary supplement is ephedra-free is not a indication of its safety."[17]

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[16] Consumers Union Dietary Supplement Survey, June 4, 2004. A total of 1,221 online surveys were conducted among a random sample of U.S. adults. Interviewing took place over May 12-17, 2004. Agreement varied little by gender, age, income or region of residence.

[17] Jill Burcum, "Your Health: Ephedra-free products loaded with new herbs of concern," Minneapolis Star Tribune, April 29, 2003.

Because of safety concerns, *Consumer Reports* urges consumers to avoid all dietary supplements marketed for weight loss, because many contain dangerous stimulants and high levels of caffeine.

Many weight loss supplements that are being marketed as "ephedra-free" contain bitter orange. Bitter orange is derived from the Seville orange and has the botanical name citrus aurantium. It appears in some foods, including orange marmalades. In dietary supplements, it appears in a concentrated form, and its active ingredient—synephrine—mimics the effects of ephedra. Synephrine stimulates the cardiovascular system, raises the heart rate, raises blood pressure, and stimulates the central nervous system. While its use has been studied in animals, there have been few studies involving human subjects.

In its May 2004 article, *Consumer Reports* profiled a 21-year-old college student studying for finals who took weight loss supplements containing bitter orange, believing they were safe because they were labeled as "ephedra-free." After three weeks of taking the product, she experienced a seizure. Her neurologist told her that the bitter orange in the supplement product was a likely cause. Since discontinuing use of the supplement, she has not experienced any more seizures.

In May, the Annals of Pharmacotherapy published a detailed case-report describing a possible association of heart failure (acute lateral-wall myocardial infarction) with the use of a dietary supplement containing bitter orange.[18]

Of course, it is difficult to extrapolate from individual reports such as these to establish definitively that a product is unsafe. However, this illustrates perfectly the inappropriate burden-shifting for safety established under DSHEA. By the time we have sufficient information on potential hazards posed by bitter orange, many consumers may have experienced serious adverse health events, including seizures or strokes. This clearly illustrates why the burden of proof for establishing that dietary supplements are safe and effective ought to be on the manufacturer—not on consumers, health professionals, consumer groups, or the government.

DSHEA LOOPHOLES PERMIT SALE AND MARKETING OF UNTESTED STEROID EQUIVALENTS

Dangerous loopholes in DSHEA and the Controlled Substances Act permit manufacturers to aggressively market and sell untested, unregulated steroid equivalents to the public, including persons under 18. A national survey conducted for the Blue Cross Blue Shield Association in 1999 found that six percent of youths ages 15 to 16 and eight percent of 17- and 18-year-olds had taken a sports supplement. Yet as we noted in *Consumer Reports* magazine in June 2001, sports-medicine researchers have only tested products like androstenedione and creatine in adults.[19] There has been no systematic testing of these drugs in minors, and for ethical reasons, such tests probably will not be conducted. For safety reasons, numerous sporting and medical

[18] Nykamp, Diane L., Fackih, M.N., and Compton, A. L., "Possible Association of Acute Lateral-Wall Myocardial Infarction and Bitter Orange Supplement," The Annals of Pharmacotherapy, May 2004, Vol. 38, p. 812-815.
[19] "Sports Supplement Dangers," Consumer Reports, June 2001, p. 40.

organizations, including the AMA and the American Academy of Pediatrics, believe that steroid precursors should be classified as Controlled Substances. Because of the safety issues involved, we support this approach, and urge Congress to regulate all steroid precursors under the Controlled Substances Act—including DHEA.

POTENTIAL FOR ADVERSE REACTIONS WITH PREEXISTING HEALTH CONDITIONS AND/OR OTHER MEDICATONS

Consumers may also experience safety problems with dietary supplements because of potential interactions with existing health conditions, such as diabetes, coronary problems or hypertension, and with other prescription or over-the counter medications they are currently taking.

According to Dr. Arthur Grollman, professor of medicine and pharmacological sciences at the State University of New York at Stony Brook:

> Interactions between herbal products and prescription or over-the-counter drugs constitutes one of the greatest risks posed by the used of botanical medicines. Botanical medicines can act through a variety of mechanisms to alter the actions and metabolism of prescription and OTC drugs.... In fact, serious adverse effects have been reported in patients taking cyclosporine or antiretroviral agents when they added St. John's wort, which caused blood levels of their life-saving drug to fall to amounts that were no longer therapeutic.
>
> The extent of herb-drug interactions is unclear, but its potential magnitude can be judged by a recent survey of medication use in the U.S. A recent survey found that among individuals over 18 years of age, 50% took at least one prescription drug during the preceding week. Among women over 65 years or older, 23% took at least five prescription drugs. 16% of those taking prescription drugs also took an herbal supplement. Thus, many Americans unknowingly risk therapeutic failures or adverse effects due to herb-drug interactions, especially older individuals who take multiple medications for chronic diseases.[20]

For these reasons, *Consumer Reports* recommends that consumers discuss the use of all dietary supplements with their physicians or health providers prior to taking them, to guard against the possibility of adverse health effects or drug reactions. However, according to the American Society of Anesthesiologists, seven in 10 consumers do not discuss the use of supplements with their doctor.

RECOMMENDATIONS

As a nation, we stand at a crossroads regarding dietary supplement safety. For the last ten years, consumers have borne the unacceptable risks and consequences of a law that allows untested

[20] Grollman, Arthur, MD. Testimony before Senate Commerce Committee hearing on dietary supplements, October 28, 2003.

supplements to be aggressively marketed and sold, with no prior safety testing and evaluation. This situation shifts the burden of proof to demonstrate supplements are safe before they can be sold from manufacturers to the government, and externalizes the costs and risks of that policy onto consumers and the health system.

We believe the burden of proof for demonstrating that a supplement does not present a "significant or unreasonable risk" should be placed on manufacturers to establish that supplements are safe before they are sold. We also believe that the existing dangers will be very difficult to address by banning or restricting individual substances or groups of substances, because such restrictions can be easily bypassed as new supplements are introduced with different ingredients or formulations.

1. **Congress should make appropriate modifications to DSHEA to create a sensible preventive safety system that ensures that dietary supplement products are reviewed for safety prior to marketing and sale. The safety system must also include effective post-marketing surveillance so that the government can take prompt safety actions as needed, including product recalls, warnings, and import alerts. Labels of dietary supplements should clearly indicate what and how much is in the package, and provide explicit warning of possible adverse effects, including herb-drug interactions.**

At a minimum, we strongly support the provisions in the "Dietary Supplement Safety Act of 2003" (S. 722) that would enable the FDA to take unsafe products off the market more quickly. S. 722 would require stimulants to be approved as new drugs, would declare foods containing unapproved stimulants to be adulterated, and prohibits the introduction into interstate commerce of a supplement containing a stimulant unless it is approved by the Secretary. These provisions would also be extremely helpful for addressing the hazards posed by other weight loss supplements that contain dangerous stimulants, and steroid precursors.

We also support the provisions in S. 722 that would authorize the Secretary of the Department of Health and Human Services (DHHS) to require the manufacturers of dietary supplements, or any ingredient in a dietary supplement to submit data demonstrating that the dietary supplement is safe. The Secretary would then be authorized to review the data and issue a determination that either the ingredient is safe and that continued marketing is approved, or that continued marketing is disapproved because either it is unsafe, or it has not been shown to be safe.

2. **Dietary supplement manufacturers should be required to report adverse events to the FDA.**

The current voluntary reporting system provides insufficient information for public health authorities to take prompt action regarding harmful products that put consumers at serious risk. We strongly support provisions in S. 722 that would require manufacturers, packers and distributors of dietary supplement products to collect, review, and report serious adverse events suffered by consumers using their products to the Secretary of the Department of Health and Human Services (DHHS), within 15 days of receiving notice of the event. In addition, the bill

would require dietary supplement manufacturers to report on all adverse events to DHHS annually.

There is broad consensus among many parties that adverse event reporting is critical to ensuring the safety of dietary supplements. In April 2004, the Institute of Medicine urged the Congress to amend DSHEA to require mandatory manufacturer reporting of serious adverse events. The American Medical Association supports this position. While noting that the requirement may not be necessary for all supplements, the Inspector General of DHHS called in its April 2001 report for mandatory reporting for some products. Also, in March 2002, the White House Commission on Complementary and Alternative Medicine Policy called for supplement manufacturers and suppliers to be required to maintain records and report serious adverse events to the agency. In the press conference at which the federal ephedra ban was announced in December 2003, Secretary of Health and Human Services Tommy Thompson stated that "it would be nice" to have authority to require mandatory adverse event reporting. Finally, even some industry trade associations have stated that they could support mandatory reporting of serious adverse events.

We believe that the FDA must be given additional resources and a resounding mandate from Congress to strengthen post-marketing surveillance of dietary supplements. As a first step, we support the provisions of S. 722 that would authorize the Secretary of DHHS to require manufacturers of dietary supplements to conduct post-market surveillance if the Secretary determines that consumer use of a manufactured dietary supplement may result in serious adverse events.

Consumers Union also support the provisions in a House measure, HR 3377, introduced by Representatives Susan Davis, John Dingell and Henry Waxman, that would enhance the FDA's authority to ensure supplements are safe, provide additional information to consumers, and require manufacturers to report adverse events.

Once again, I thank the Chairman, Ranking Member Durbin and the Committee for the opportunity to testify, and I look forward your questions and comments.

BEFORE THE

SUBCOMMITTEE ON OVERSIGHT OF GOVERNMENT MANAGEMENT, RESTRUCTURING AND THE DISTRICT OF COLUMBIA

SENATE COMMITTEE ON GOVERNMENTAL AFFAIRS

UNITED STATES SENATE

Testimony of Anthony Young
General Counsel
American Herbal Products Association

June 8, 2004

My name is Anthony Young. I am a partner in the law firm Kleinfeld, Kaplan & Becker, LLP and I serve as general counsel to the American Herbal Products Association (AHPA), the national trade association and voice of the herbal products industry. AHPA serves its members by promoting the responsible commerce of products which contain herbs and which are marketed as dietary supplements and are used to enhance health and quality of life. AHPA's president, Michael McGuffin, who testified before this Subcommittee two years ago, would have testified here today but for a pre-existing commitment with the Food and Drug Administration's Food Advisory Committee. I am pleased to respond in his place on behalf of AHPA to the questions posed by the Subcommittee.

The purpose of this hearing is to examine the challenges and successes the Food and Drug Administration has experienced since the passage of the Dietary Supplement Health and Education Act of 1994 ("DSHEA") which established a new regulatory framework for dietary supplements. Information generated from this hearing will be used to assess what if any steps are needed to make the FDA's regulation of dietary supplements more effective.

While DSHEA created a new regulatory framework for dietary supplements, the fundamental principles of the prior law did not change. Thus, it is a crime under the Federal Food, Drug, and Cosmetic Act ("FFDCA") to sell an adulterated (contaminated or dangerous) or misbranded (falsely or misleadingly labeled) dietary supplement, just as it has been since 1938. And DSHEA empowered FDA to regulate potentially dangerous dietary supplements and to proceed summarily against dietary supplements that pose an imminent hazard for consumers. This authority is complemented by that of the Federal Trade Commission under the Federal Trade Commission Act, which can and does act

against dietary supplements that are advertised falsely, or that make misleading claims or are otherwise unfair or deceptive. Most states have laws that track these federal laws.

DSHEA was legislation that was sought by the dietary supplement industry. Industry sought a change to the FFDCA that would direct the FDA to recognize their products and require FDA to prove a dietary supplement to be adulterated if that was FDA's position. Those goals were achieved. In addition, DSHEA gave FDA significant regulatory authority over dietary supplements.

FDA has used its regulatory authority substantially and effectively over the past ten years. Regulations have been promulgated for nutrition labeling (the Supplement Facts panel on dietary supplements), health claims and nutrient content claims, statements of nutritional support (structure function claims), notification of structure function claims, and premarket notification of new dietary ingredients proposed for use in dietary supplements.

In addition, FDA last year proposed regulations to set forth current Good Manufacturing Practices (cGMP) for dietary supplements. A framework for this proposal was first provided to FDA by AHPA and the other trade associations of this industry in 1995. FDA's proposal was a long time in coming and AHPA and other trade associations have presented comprehensive, consensus-based comments on FDA's proposal.

In the enforcement arena, FDA this year banned ephedrine-alkaloid containing ingredients from dietary supplements. That action was another that was a long time in coming. AHPA interacted with FDA on ephedra years before DSHEA became law. And AHPA since before DSHEA became law recommended cautionary labeling for ephedra-containing dietary supplements. These positions were set forth in FDA's ephedra hearings in 1995 and 1996 and thereafter.

FDA this year also banned androstenedione from dietary supplements. FDA determined this ingredient is not a dietary supplement ingredient, as defined by DSHEA, and that if it is, no new dietary ingredient notification has been made to FDA, as required by DSHEA. This is another position that was a long time in coming. FDA's androstenedione decision and position provides important guidance to industry with respect the nature of the ingredients that DSHEA permits in dietary supplements.

Proposed cGMP regulations, and enforcement action on ephedra and on androstenedione were all accomplished by FDA under the leadership of Dr. Mark McClellan. Dr. McClellan was an activist Commissioner with respect to dietary supplements and AHPA has expressed its endorsement of Dr. McClellan's resolve to identify important dietary supplement issues and address them forthrightly.

As we approach the tenth anniversary of DSHEA, I believe that much of the dietary supplement industry recognizes that FDA's ban of ephedra and androstenedione, which

effectuate DSHEA's enforcement, are as important to the industry and the acceptance of dietary supplements by the public as are FDA's various other regulatory initiatives.

Companies that recognize and follow the law understand that fair and effective enforcement is the only way to assure that legitimate competitors can survive and grow in a regulated environment. Against this background, it is a fact that FDA's enforcement of DSHEA was encouraged by the dietary supplement industry through its unified endorsement of earmarked dietary supplement enforcement funding. You can see the effect of this funding in FDA's 2002 and 2003 reports on dietary supplement enforcement. The enforcement efforts they report has been substantial and effective. These enforcement activities are an essential component of the DSHEA regulatory scheme.

Mandatory Adverse Event Reporting for Dietary Supplements.

At its October 2, 2002 meeting, AHPA's Board of Trustees determined that AHPA should petition FDA to promulgate regulations requiring that reports of serious adverse experiences associated with dietary supplements that come to the attention of manufacturers be reported to FDA. That petition was filed with FDA on March 20, 2003. While AHPA's petition has not been rejected by FDA, both Commissioner McClellan and Acting Commissioner Crawford have stated that FDA has determined it does not presently have the legal authority to require such reporting. Accordingly, AHPA supports a change in the law to provide FDA with the authority to require serious adverse events associated with the use of dietary supplements to be reported to it.

While many dietary supplement manufacturers have systems in place to collect and address dietary supplement adverse experience reports that come to their attention, those systems are internal and there is presently no place where the experiences of each company are collected and assessed. Collection of serious adverse event report information in one place serves the salutary purpose of aggregating information that may not appear meaningful when addressed at one company. That information can then be assessed to determine whether there are events that constitute signals with respect to potential issues with dietary supplements or their ingredients.

AHPA's AER petition sought the associated protections for AER reports that are now provided to pharmaceutical and medical device manufacturers. The current rules that govern submission to FDA of serious adverse events associated with drugs (specifically, prescription drugs that are not new drugs, as codified at 21 CFR 310.305; and prescription drugs that are subject to new drug applications, as codified at 21 CFR 314.80), provide certain protections for the submitting drug companies. Any rules that might be developed for serious adverse events for dietary supplements should include these same protections, as follows:

PROTECTION 1: Submission of a serious adverse event report does not constitute an admission. The existing rules for drugs specifically state that neither a submission of

an adverse event report to FDA nor a release of information about the submission necessarily reflects a conclusion that there existed a causal relationship between the use of the drug and the adverse event.

310.305 (g) *Disclaimer and No Admission.* A report or information submitted by a manufacturer, packer, or distributor under this section (and any release by FDA of that report or information) does not necessarily reflect a conclusion by the manufacturer, packer, or distributor, or by FDA, that the report or information constitutes an admission that the drug caused or contributed to an adverse effect. The manufacturer, packer, or distributor need not admit, and may deny, that the report or information submitted under this section constitutes an admission that the drug caused or contributed to an adverse effect.

314.80 (k) *Disclaimer.* A report or information submitted by an applicant under this section (and any release by FDA of that report or information) does not necessarily reflect a conclusion by the applicant or FDA that the report or information constitutes an admission that the drug caused or contributed to an adverse effect. An applicant need not admit, and may deny, that the report or information submitted under this section constitutes an admission that the drug caused or contributed to an adverse effect. For purposes of this provision, the term ''applicant'' also includes any person reporting under paragraph (c)(1)(iii) of this section.

The FFDCA now contains a provision that confirms this protection for drugs and also provides this protection for dietary supplements and food. 21 USC 379(v) states:

"With respect to any entity that submits or is required to submit a ***safety report*** *or other information in connection with the safety of a product (including a product that is a food, drug, device,* ***dietary supplement****, or cosmetic) under this chapter (and any release by the Secretary of that report or information), such report or information shall not be construed to reflect necessarily a conclusion by the entity or the Secretary that the report or information constitutes an admission that the product involved malfunctioned, caused or contributed to an adverse experience, or otherwise caused or contributed to a death, serious injury, or serious illness. Such an entity need not admit, and may deny, that the report or information submitted by the entity constitutes an admission that the product involved malfunctioned, caused or contributed to an adverse experience, or caused or contributed to a death, serious injury, or serious illness"*(emphasis added).

Therefore, any legislation to empower FDA to require serious adverse event reporting for dietary supplements should provide that such reports Act shall be deemed a "safety report" for purposes of Section 756 of the FFDCA (21 USC 379(v).

PROTECTION 2: The identity of the person with whom the AE was associated is private. The existing rules for drugs specifically state that the firm that submits an adverse event report should not identify the individual who is the subject of the report. The existing rules also state that names and identifying characteristics of all persons associated with a reported adverse event are not to be disclosed under the regulations related to the Freedom of Information Act and the Privacy Act of 1974.

310.305 (e) *Patient privacy.* Manufacturers, packers, and distributors should not include in reports under this section the names and addresses of individual patients; instead, the manufacturer, packer, and distributor should assign a unique code number to each report, preferably not more than eight characters in length. The manufacturer, packer, and distributor should include the name of the reporter from whom the information was received. Names of patients, individual reporters, health care professionals, hospitals, and geographical identifiers in adverse drug experience reports are not releasable to the public under FDA's public information regulations in Part 20 of this chapter.

314.80 (h) *Patient privacy.* An applicant should not include in reports under this section the names and addresses of individual patients; instead, the applicant should assign a unique code number to each report, preferably not more than eight characters in length. The applicant should include the name of the reporter from whom the information was

received. Names of patients, health care professionals, hospitals, and geographical identifiers in adverse drug experience reports are not releasable to the public under FDA's public information regulations in part 20.

Legislative language can address this issue by reference to the Privacy Act of 1974 which contains the language that establishes this protection for personal information as follows:

§552a. Records about individuals.

For purposes of this section

(1) the term "agency" means agency as defined in section 552(e) (FOOTNOTE 1) of this title;

(2) the term "individual" means a citizen of the United States or an alien lawfully admitted for permanent residence;

...

(4) the term "record" means any item, collection, or grouping of information about an individual that is maintained by an agency, including, but not limited to, his education, financial transactions, medical history, and criminal or employment history and that contains his name, or the identifying number, symbol, or other identifying particular assigned to the individual, such as a finger or voice print or a photograph;

...

(b) Conditions of Disclosure.

No agency shall disclose any record which is contained in a system of records by any means of communication to any person, or to another agency, except pursuant to a written request by, or with the prior written consent of, the individual to whom the record pertains, unless disclosure of the record would be -

(1) to those officers and employees of the agency which maintains the record who have a need for the record in the performance of their duties;

(2) required under section 552 of this title;

(3) for a routine use as defined in subsection (a)(7) of this section and described under subsection (e)(4)(D) of this section;

(4) to the Bureau of the Census for purposes of planning or carrying out a census or survey or related activity pursuant to the provisions of title 13;

(5) to a recipient who has provided the agency with advance adequate written assurance that the record will be used solely as a statistical research or reporting record, and the record is to be transferred in a form that is not individually identifiable;

(6) to the National Archives and Records Administration as a record which has sufficient historical or other value to warrant its continued preservation by the United States Government, or for evaluation by the Archivist of the United States or the designee of the Archivist to determine whether the record has such value;

(7) to another agency or to an instrumentality of any governmental jurisdiction within or under the control of the United States for a civil or criminal law enforcement activity if the activity is authorized by law, and if the head of the agency or instrumentality has made a written request to the agency which maintains the record specifying the particular portion desired and the law enforcement activity for which the record is sought;

(8) to a person pursuant to a showing of compelling circumstances affecting the health or safety of an individual if upon such disclosure notification is transmitted to the last known address of such individual;

(9) to either House of Congress, or, to the extent of matter within its jurisdiction, any committee or subcommittee thereof, any joint committee of Congress or subcommittee of any such joint committee;

(10) to the Comptroller General, or any of his authorized representatives, in the course of the performance of the duties of the General Accounting Office;

(11) pursuant to the order of a court of competent jurisdiction; or

(12) to a consumer reporting agency in accordance with section 3711(f) of title 31.

Therefore, any legislation providing FDA authority to mandate the reporting of serious adverse events for dietary supplements should require FDA to deem such reports to be a "record" about an "individual" under the Privacy Act of 1974.

PROTECTION 3: Identifying information about persons associated with AERs should not be subject to disclosure in response to a request, demand, or order. For drugs, medical devices and biologics, FDA established regulations that were meant to encourage healthcare providers to submit AERs associated with these products to the MedWatch system.

21 CFR 20.63. The names and any information that would identify the voluntary reporter or any other person associated with an adverse event involving a human drug, biologic, or medical device product shall not be disclosed by the Food and Drug Administration or by a manufacturer in possession of such reports in response to a request, demand, or order. Information that would identify the voluntary reporter or persons identified in the report includes, but is not limited to, the name, address, institution, or any other information that would lead to the identities of the reporter or persons identified in a report. This provision does not affect disclosure of the identities of reporters required by a Federal statute or regulation to make adverse event reports. Disclosure of the identities of such reporters is governed by the applicable Federal statutes and regulations.

The Freedom of Information Act (FOIA) is a basis for the above rule. FOIA contains language that protects medical information from disclosure:

5 U.S.C. Sec. 552. - Public information; agency rules, opinions, orders, records, and proceedings
(a) Each agency shall make available to the public information as follows:

...

(3) (A) Except with respect to the records made available under paragraphs (1) and (2) of this subsection, and except as provided in subparagraph (E), each agency, upon any request for records which (i) reasonably describes such records and (ii) is made in accordance with published rules stating the time, place, fees (if any), and procedures to be followed, shall make the records promptly available to any person.

...

(b)
This section does not apply to matters that are -

...

(6) personnel and medical files and similar files the disclosure of which would constitute a clearly unwarranted invasion of personal privacy...

Therefore, any legislation that empowers FDA to mandate the serious adverse event reports for dietary supplements should propose to reference the Freedom of Information Act and deem such reports "medical files or similar files the disclosure of which would constitute a clearly unwarranted invasion of personal privacy" under that law, unless redacted to remove personal identifying information.

PROTECTION 4: Under current Food and Drug Administration regulations for reporting adverse events associated with drugs, medical devices and biologics, the privacy and personal identifying information protections of the regulations are declared to be preemptive of State and federal law.

21 CFR Sec. 20.63(f)(2) Preemption. No State or local governing entity shall establish or continue in effect any law, rule, regulation, or other requirement that permits or requires disclosure of the identities of the voluntary reporter or other person identified in an adverse event report except as provided in this section.

FDA's establishment of the above regulation did not implement any specific statute. Rather, the agency used its general authority in promulgating this rule. Nonetheless, this provision has been firmly upheld by courts as preemptive of State or federal procedural rules for the production of documents required to be produced to parties in litigation.

Therefore, legislation to empower FDA to require reporting of serious adverse events for dietary supplements should provide that no State or local governing entity shall establish or continue in effect any law, rule, regulation, or other requirement that permits or requires disclosure of the identities of the voluntary reporter or other person identified in an adverse event report except as provided in this section.

PROTECTION 5: In the past, FDA has released information about the frequency and nature of serious adverse events associated with dietary supplements prior to that information being made available to the companies whose products have been said to be associated with the event. While FDA has attempted to remedy this situation, legislation empowering FDA to require reporting of serious adverse events for dietary supplements should assure that FDA promptly shares information with affected companies, require that FDA correct frank errors in its system that that FDA make information on dietary supplement adverse events available on the same basis as it makes such information available for prescription drugs.

AHPA was active in communicating concerns about the disclosure of dietary supplement adverse event reporting information even before the implementation of the SN/AEMS reporting system that was abandoned by FDA in 2002. For example, on February 11, 1998, AHPA submitted a letter to FDA's Robert Lake and to Dr. Elizabeth Yetley to discuss the imminent placement of the SN/AEMS on FDA's website. Included in this letter was AHPA's expressed concern that manufacturers' access to information posted on the SN/AEMS website about their products be made readily available and AHPA provided specific suggestions as to how this issue could be addressed. In addition, AHPA addressed a letter to FDA Chief Counsel Daniel Troy and to Dr. Christine Taylor on March 28, 2002, to request that certain reports be excluded from kava entries on the SN/AEMS site since FDA had information that the product that was the subject of these reports did not contain kava, and in fact contained an illegal drug.

To the best of AHPA's institutional memory, the only formal response AHPA received to these communications was to the last mentioned. On August 29, 2002, the date of FDA's telephone conference announcing the new system, CAERS, Dr. Taylor acknowledged receipt of AHPA's correspondence and informed AHPA that the Center had decided to remove the SN/AEMS reports from FDA's website.

AHPA is concerned about the FDA's practice in the past to make summary adverse event reporting information available on its website. Such reports are not made available by FDA for prescription drugs. AHPA does not oppose the public availability of information regarding dietary supplement adverse experience reports. AHPA does object to dietary supplements being treated differently than drugs and other regulated products.

Accordingly, any legislation regarding serious adverse event reporting for dietary supplements should address these issues.

DSHEA's New Dietary Ingredient Premarket Notification Requirement.

'Old' and 'New' Under the FFDCA

When the FFDCA was passed in 1938, its new drug approval provision was intended to respond to the tragic marketing of Elixir of Sulfanilamide – which mixed a safe and effective drug in a good tasting but otherwise poisonous ethylene glycol solution that led to over 100 fatalities. Nonetheless, the FFDCA allowed drugs then on the market to remain on the market – and these existing drugs were referred to in the trade as "grandfathered" drugs. The products to be regulated under the law's new requirement that safety be demonstrated and approval granted prior to marketing were referred to as "new drugs." If a "grandfathered" drug was alleged to be harmful or mislabeled, it could be proceeded against by FDA under the law's adulteration and misbranding provisions.

Similarly, when the Food Additive Amendments of 1958 became law, ingredients then on the market were permitted to remain on the market if they were "generally recognized as safe ("GRAS")" for use as food. This was accomplished in the definition of "food additive" which excluded ingredients which met the definition of GRAS. If an additive was alleged not to be safe, it could be proceeded against under the law's prohibition of unapproved food additives in food. The law also exempted ingredients that had received a prior sanction from FDA or USDA for use in food.

The Medical Device Amendments of 1976 also contained a form of "grandfather" clause. That act required that anyone first introducing a product after enactment submit a premarket notification. Devices already on the market were reviewed in the context of a medical device classification process. Pre-amendment devices that were alleged to be dangerous or mislabeled could be proceeded against under the FFDCA adulteration or misbranding provisions.

'Old' and 'New' Under DSHEA

The passage of the DSHEA in 1994 adopted an approach that was consistent with these earlier laws with respect to "old" and "new" ingredients. Thus, DSHEA provided a statutory definition of a "new dietary ingredient" and imposed upon such ingredients the requirement that a notification be submitted prior to their use in dietary supplements. As was the case with new drugs, food additives and post-enactment medical devices, Congress "grandfathered" old dietary ingredients and any such old ingredients that were alleged to be unsafe or mislabeled could be proceeded against under the adulteration and misbranding provisions of the FFDCA. This is the process followed by FDA with respect to ephedrine alkaloid-containing dietary supplements.

The difference between an old and a new dietary ingredient, according to DSHEA, is simply a matter of whether the particular ingredient was already available for sale in the United States prior to the date of passage of the law. DSHEA defined a "new dietary ingredient" as follows:

The term "new dietary ingredient" means a dietary ingredient that was not marketed in the United States before October 15, 1994 and does not include any dietary ingredient which was marketed in the United States before October 15, 1994.

DSHEA controls the introduction of new dietary ingredients by defining as adulterated any dietary supplement product that contains a new dietary ingredient, including a known ingredient which has been "chemically altered," unless FDA is notified prior to marketing such product. The requirement is stated in Section 8 of DSHEA, which amended Section 413(a) of the FFDCA as follows:

A dietary supplement which contains a new dietary ingredient shall be deemed adulterated under section 402(f) unless it meets one of the following requirements:

(1) *The dietary supplement contains only dietary ingredients which have been present in the food supply as an article used for food in a form in which the food has not been chemically altered.*

(2) *There is a history of use or other evidence of safety establishing that the dietary ingredient when used under the conditions recommended or suggested in the labeling of the dietary supplement will reasonably be expected to be safe and, at least 75 days before being introduced or delivered for introduction into interstate commerce, the manufacturer or distributor of the dietary ingredient or dietary supplement provides the Secretary* [of Health and Human Services] *with information, including any citation to published articles, which is the basis on which the manufacturer or distributor has concluded that a dietary supplement containing such dietary ingredient will reasonably be expected to be safe.*

Accordingly, there are two stated conditions that control the market entry of new dietary ingredients: (1) there must be an evidentiary basis that supports a reasonable expectation of safety for the marketed use, and (2) FDA must be provided with information to support this expectation 75 days prior to marketing (a "75-day notice" or "premarket notification").

In actual practice there is a third condition that controls the introduction of a new dietary ingredient: FDA must accept that the information provided is sufficient to assure that the ingredient is reasonably expected to be safe under proposed conditions of use. This acceptance is not directly addressed in either the law itself or the governing regulations. Indeed, there is no legislative record that FDA ever sought premarket approval authority for new dietary ingredients. Instead, FDA sought notification only, probably on the theory that saying "no" is easy, saying nothing is neutral, and saying "yes" would become as burdensome and difficult, administratively, as it had by then become for food additives and new drugs. Thus, FDA has developed the practice of responding in various ways to

notices it deems to be insufficient, while simply filing (usually without comment) in the docket FDA has established for these notices those found to have met the statutory and regulatory requirements.

When AHPA last counted, only about 45 percent of those new dietary ingredient premarket notifications that were submitted to FDA were filed in a manner that indicated the ingredients could proceed to market. FDA's docket has recently been updated since AHPA last counted, but there is no reason to believe the ratio of rejection versus acceptance has changed. AHPA's conclusion, and my conclusion as a lawyer who counsels company with respect to such filings, is that this DSHEA provision works, that FDA takes its review responsibility seriously, and that companies respecting this provision are diligent in providing information to FDA and in responding to any questions FDA may have.

But FDA has only received and reviewed a total of 188 premarket notification submissions, and some of these are resubmissions of notifications that were initially "rejected" by FDA. FDA's action with respect to androstenedione firmly establishes the role of the new dietary ingredient provision under DSHEA and the important role this provision can play as gatekeeper for new dietary ingredients. At the same time, it is clear that FDA needs to monitor marketed dietary supplements to catch new dietary ingredients that have not met DSHEA's requirements before those ingredients become established in the marketplace. This is not a difficult task – one only needs to read the advertising for such products.

For the future, FDA needs to pay as much attention to ingredients that are new that come to market without observing the requirements of DSHEA's premarket notification provision as it devotes to those ingredients that are submitted by those who observe the requirements of law. To do otherwise is unfair and disrespectful of the law the law abiding. Not enforcing the new DSHEA's new dietary ingredient provision rewards lawbreakers at the expense of those who observe the law.

The analogy we like to use with respect to premarket notification of new dietary ingredients is that of a toll road on a eight lane turnpike that has only one toll booth on one lane. All who pass are required to pay the toll, but that takes time and money, so only those who decide to observe the law and pay the toll do so. No government could operate a Turnpike Authority that way and it is no way for the FDA to effectuate DSHEA's new dietary ingredient provision.

AHPA appreciates the opportunity to appear at this hearing and to provide this testimony.

United States Senate

Committee on Governmental Affairs

Testimony of Bruce Silverglade
Director of Legal Affairs
Center for Science in the Public Interest

HEARINGS ON THE DIETARY SUPPLEMENT SAFETY ACT
HOW IS FDA DOING 10 YEARS LATER?

* * *

June 8, 2004

Hart Senate Office Building
Washington, D.C.

Good afternoon. I am Bruce Silverglade, Director of Legal Affairs, of the Center for Science in the Public Interest (CSPI). With me today is Ilene Ringel Heller, senior staff attorney at CSPI. We are pleased to have this opportunity to testify on the Dietary Supplement Safety Act: How is FDA Doing 10 Years Later? CSPI is a nonprofit consumer advocacy organization based in Washington, D.C. We were founded in 1971 and are now supported by more than 750,000 subscribers to our *Nutrition Action Healthletter*, membership donations, and foundation grants. We accept no money from industry or government. Most of our current work focuses on improving the safety and nutritional quality of our food supply and we have worked extensively to ensure that dietary supplements are safe and honestly labeled.

I. Introduction

It has been 10 years since the enactment of the Dietary Supplement Health and Education Act of 1994 (DSHEA). It is certainly appropriate to review the impact of this legislation on consumers and discuss the need for reforms such as those included in S. 722, the Dietary Supplement Safety Act. We support this legislation and urge Congress to enact it this year. As I will explain in a moment, however, Congress needs to extend attentional protections to consumers that are not included in this bill.

Since 1994, Americans have become increasingly cognizant of the benefits that many dietary supplements can provide. Today, half of all American adults take vitamin or mineral supplements, and one in three has tried herbs. One of the reasons for this trend is that many Americans are disenchanted with a medical establishment that increasingly funnels patients through doctors' offices as if they were on an assembly line. In addition, consumers hear more and more about promising research that some dietary supplement ingredients may hold the key to preventing cancer and other dreaded diseases. Our publication, *Nutrition Action Healthletter*, regularly reports on these developments. In light of such factors, many Americans want to take control of their own health.

Many supplements are undoubtedly beneficial. For example, millions of Americans need to consume more calcium to help prevent osteoporosis. Women of childbearing age who consume sufficient amounts of folic acid can reduce the risk of neural tube defects in their unborn children. A growing number of studies suggest that saw palmetto can help men with benign enlarged prostates. In brief, more and more Americans are getting the message that dietary supplements can play an important role in maintaining good health and can sometimes provide a valuable adjunct to conventional medical treatment.

Unfortunately benefits have not been established for all supplements, and many consumers cannot determine on their own which products are worth consuming and which are nothing more than 21st century snake oil or even dangerous. As Americans increasingly use

supplements to promote their health, it is critical that Congress ensure that such products are safe and that label claims are accurate and scientifically valid.

II. History of DSHEA

Supplement manufacturers themselves deserve much of the blame for unsafe ingredients, poor quality products, and misleading promotional practices that now plague the marketplace. In 1994, the industry successfully lobbied Congress for legislation that made it more difficult for the Food and Drug Administration (FDA) to do its job. Health-food retailers were enlisted to whip consumers into a frenzy by telling them, falsely, that the FDA was about to require physicians' prescriptions for ordinary vitamins. Consumers were then urged to write their members of Congress in support of legislation drafted by industry lobbyists that would curtail the FDA's authority. (The same ploys are now being used to organize opposition to S. 722.)

Congress responded by passing the DSHEA. The 1994 law has led to short-term economic gains for supplement producers, but has caused a myriad of problems for consumers, including unsafe ingredients, low quality products, and a marketplace free-for-all of misleading claims. I will discuss each of these matters in turn.

III. Safety Problems

DSHEA changed the prevailing approach to product safety under the Federal Food, Drug, and Cosmetic Act. The manufacturers of food additives, drugs, and medical devices must prove that their products are safe before they can be sold. DSHEA, however, freed manufacturers from the responsibility of demonstrating that supplement ingredients are safe before they are sold. Although the FDA still has the authority to take dangerous products off the shelves, it must first prove that the products pose a "significant or unreasonable risk." That means that the FDA must build a case before it can take action and people are often injured in the interim.

In addition, manufacturers have no legal obligation to turn over reports of adverse health reactions to the FDA. Such information is essential to ascertaining whether a product is causing harm, especially in the absence of any pre-market approval system. Without such data, it is extremely difficult for FDA to obtain both the quality and quantity of information needed to demonstrate that a product causes a "significant or unreasonable risk" under current law.

Thus, as a practical matter, the FDA has not been able to effectively utilize the authority granted to it by DSHEA. Consequently, the agency has been forced to rely on woefully inadequate remedies such as issuing public warnings and requesting voluntary recalls. Clearly, a more effective regulatory approach must be found if consumers are to be protected from unsafe products.

Now we all know that the FDA banned ephedra this year (10 years after it issued its first medical bulletin that raised health concerns). But as newspaper editorial boards across the country noted, ephedra simply epitomized why the current law fails to protect consumers from hazardous products. The *Washington Post* called DSHEA a "truly terrible law" and the *New York Times* called the ephedra ban "not enough" and urged Congress to "revise the ill-conceived 1994 legislation."

The agency has tried to put the best light on what most FDA staff would acknowledge privately is a bad law. For example, media accounts of a speech by former FDA Commissioner Mark McClellan state that the agency is becoming more aggressive in gathering safety evidence about other supplements beyond ephedra that it views as potentially harmful. The FDA's statements to the media specifically mentioned that the agency was tracking three weight loss supplements posing risks similar to ephedra: bitter orange, aristolochic acid, usnic acid — as if this were an important new development. However, aristolochic acid was already the subject of an FDA consumer advisory in 2001, a health professionals alert in May 2000, and an import alert in July 2000 and April 2001. Usnic acid was an ingredient in the dietary supplement LipoKinetix that FDA warned consumers not to use in 2001.

Since 2001, FDA's Compliance Program has instructed inspectors to collect samples of both aristolochia and bitter orange so that FDA can "evaluate the possible health risks." It is interesting to note that the 2001 compliance program which is still in effect, states that "At this time, no regulatory/enforcement actions are planned or anticipated for products containing these ingredients." Thus while FDA may be "talking a new talk, it is walking the same walk." The root problem is that the 1994 law that the FDA must administer relies on manufacturers to determine whether a product is safe and then prevents the agency from acting promptly and decisively when problems arise.

The FDA takes the same all-talk, no action, approach with respect to other types of dietary supplements as well. For example, St. John's wort, used to treat mild cases of depression (its purported benefits are controversial and not established) can interact with oral contraceptives and reduce their effectiveness. It may also interfere with a protease inhibitor used to treat HIV infection and drugs used to treat heart disease or to prevent conditions such as transplant rejection. The FDA has issued an alert about such problems, but how many consumers are actually aware of that information?

The safety problem is compounded by manufacturers that sell traditional herbal medicines for non-traditional purposes. A herb that may have produced minimal side effects when used for a traditional purpose may cause severe adverse reactions when used for a different purpose. Consumers may assume that the herb is safe because it has been used in China for hundreds of years. What people do not realize is that while a botanical may be safe for some uses, it may not be safe for other uses.

Also, many consumers do not understand that if a supplement such as a herbal medicine has health benefits, it probably also has health risks simply because it is

pharmacologically active. Many prescription drugs come from plants, and the dangers of prescription drugs are well known. But supplement consumers often mistakenly believe that "if it is natural it must be safe." Unfortunately, nothing could be further from the truth. All of these considerations call for a reexamination of the regulatory framework set out in DSHEA to ensure supplement safety.

S. 722 would help address some of these problems by requiring that manufacturers report serious adverse reactions to the FDA. The agency could then insist that the manufacturer demonstrate the safety of the product or take it off the market. Under DSHEA, the FDA has no authority to require that firms report consumer complaints about adverse reactions. Instead, the agency must rely on companies to voluntarily report problems. The extent of under reporting is illustrated by the fact that in just one private law suit involving a weight-loss product containing ephedra, lawyers uncovered 3,500 complaints that had never been forwarded to the FDA. Clearly, this situation must change.

S. 722 would also require pre-market approval for stimulants, one category of dietary supplements that pose some of the most severe hazards. These are useful reforms that we support. But Congress should go further:

- Safety standards for dietary supplements intended for use by children, pregnant women, the elderly, and other vulnerable sub-populations determined by the agency to be at particular risk should be raised and manufacturers should be required to submit evidence of safety to FDA before such products are sold.

- In addition, manufacturers should only be permitted to make safety-related claims in labeling and advertising if the agency has determined by regulation, prior to marketing, that the particular ingredient satisfies the safety standard for that category of supplements.

These steps, together with the provisions incorporated in S. 722, would go a long way to ensuring that supplements in the U.S. are safe.

IV. Good Manufacturing Practice Regulations

The current law fails to require the supplement industry to adhere to strict quality standards. Such rules, which have been in place for over-the-counter and prescription drugs for decades, would help ensure that products are, among other things, free of contaminants. Poor quality has been a nagging concern for the industry. For example, an independent study by Consumerlab.com revealed that eight of 21 brands of ginseng had unacceptable levels of pesticide residues. Two brands contained residues at more than 20 times the amount considered safe. Further, two other brands tested contained high levels of lead. In addition, some dietary supplements containing calcium made from bone meal and consumed by pregnant women have had high levels of lead that potentially could harm the fetus. Others supplements sold to improve brain function contain concentrated raw brain tissue from cows.

That practice is considered inappropriate given the prevalence of mad-cow disease in Europe and the potential that it can lead to a new variety of Creutzfeldt-Jakob disease (CJD) in humans.[1]

DSHEA authorized the FDA to issue Good Manufacturing Practice Regulations (GMPs) based on those established for foods.[2] That requirement is a bit odd because dietary supplements more closely resemble non-prescription drugs and should be manufactured to the same quality standards as those products. In any event, GMPs help ensure that the product contains the precise amounts of ingredients specified on the label and specify production processes that reduce the chances that products are contaminated with undesirable substances.

The FDA issued an Advance Notice of Proposed Rulemaking on GMPs in 1997 and sent a proposed rule to the Office of Management and Budget (OMB) on November 8, 2000.[3] However, on February 1, 2001, after the Bush Administration took office, the FDA withdrew the proposed rule, thus delaying publication of the proposal.[4] After OMB review by the current administration, the FDA ultimately proposed a GMP rule on March 13, 2003. However, many segments of the industry still opposed the proposed rule as too strict. Consequently, a final rule has not yet been issued.

- Given this track record, Congress should intervene and require that an adequate GMP rule be finalized by a deadline imposed by Congress.

I should note that while the development of GMPs is important, they do not ensure that supplement ingredients themselves are safe and effective for their intended use. For example, even if all St. John's wort tablets manufactured in the U.S. met rigorous GMPs, consumers could still suffer adverse health consequences if they consumed this herbal supplement while also taking various prescription medications.

V. Misleading Labeling Claims

The 1994 law allows manufacturers to make health-related labeling claims – so-called structure/function claims – without first proving to the FDA that the claims are valid. An avalanche of misleading claims has resulted. One can find products in health-food stores for

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[1] Geoffrey Cowley, *Cannibals to Cows: The Path of a Deadly Disease,* Newsweek, Mar. 12, 2001 at 53, 61.

[2] FDCA § 402(g)(2), 21 U.S.C. § 342(g)(2).

[3] Office of Management and Budget, Office of Information and Regulatory Affairs *Regulations Pending and Reviews Completed Last 30 Days* <http:///www.whitehouse.gov/library/omb> (visited Feb. 9, 2001).

[4] *Id.*

almost every ailment under the sun, ranging from improving sex drive to burning fat. But even some nationally advertised, brand-name products sold in large supermarket chain stores have crossed the line.

For example, one of the most popular herbs, garlic, has been widely promoted for maintaining heart health and/or healthy cholesterol levels. Typical claims include statements such as "regular consumption of garlic may help promote healthy heart function and regulate cholesterol levels." However, a review commissioned by the Agency for Healthcare Research and Quality (AHRQ) concluded that garlic does not appear to have benefits that endure beyond six months and "does not appear to offer long-term protection against cardiovascular disease."[5] The inability of garlic supplements to reduce cholesterol levels beyond six months is crucial because it is the *prolonged* elevation of blood cholesterol levels that raises the risk of cardiovascular disease. Thus, a product that does not work beyond six months is virtually useless. (Preliminary evidence, however, still holds out hope that garlic pills may help prevent blood clots, another risk factor in heart disease.)

FDA has recently begun challenging a few structure/function claims as misleading. But without the authority to demand that such claims be authorized prior to marketing, the FDA is unable to protect the public; the agency lacks the resources to engage in lengthy "after-the-fact" litigation against the hundreds, perhaps thousands, of products that make misleading claims.

While the law still requires companies to get FDA pre-market authorization to make expressed disease prevention claims, often referred to as "health claims," firms are free to make a myriad of other *health-related* structure/function claims by simply notifying the agency within 30 days *after* marketing a product. This problem is not addressed by S. 722. We hope it could be. Specifically,

- Structure/Function claims should be subject to the same procedures required in the law for "health claims" for foods. The Act requires that the agency determine, through notice and comment rulemaking, that health claims for foods be supported by "significant scientific agreement."[6]

The distinctions between the types of claims requiring FDA pre-market authorization and those that do not are often meaningless to consumers. For example, under FDA rules that attempt to implement this portion of DSHEA, companies can claim that a supplement maintains healthy lung function but cannot say, without first obtaining FDA approval, that a

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[5] AHRQ, *Garlic Effects on Cardiovascular Risks and Diseases, Protective Effects Against Cancer, and Clinical Adverse Effects* (Oct. 2000).

[6] In December 2002, the FDA attempted to reinterpret that statutory requirement. That action had been challenged in court in 2003, See, *Public Citizen v. Food and Drug Administration*, Federal District Court for the District of Columbia, Docket No. 03-1962.

supplement maintains healthy lungs in smokers.[7] However, in both cases, consumers are likely to assume that the products will decrease their risk of lung disease.

As the General Accounting Office (GAO) noted, "FDA conducted nine focus groups on dietary supplement labeling in three cities around the country. Among other things, this research found, 'there was no indication that participants differentiated at all between structure/function claims and health claims.' . . .As such, consumers incorrectly view claims to maintain health (structure/function claims) as claims to reduce the risk of, or treat a disease. Consequently, we believe that consumers may attempt to treat a disease with a product not capable of producing this benefit."[8]

This loophole in the law is particularly disturbing considering that the presumed benefits of some supplements are based on anecdotal evidence or studies that were not conducted in accordance with modern scientific techniques. Moreover, many, if not most, companies making health-related structure/function claims have reportedly failed to even comply with the weak FDA notification requirement contained in DSHEA.[9] Not surprisingly, many outlandish claims on supplements have appeared on store shelves since DSHEA was enacted.

VI. Conclusion

Unsafe ingredients, poor quality products, and misleading claims may now be adversely affecting sales; recent figures suggest that some supplement sales are declining. The industry is running a public relations and lobbying campaign in an attempt to woo consumers back to supplements. But by continuing to demand weak regulation, the dietary supplement industry is essentially "shooting itself in the foot." And, as more and more adverse reactions to supplements are reported in the media, and misleading health-related claims proliferate, consumers will likely turn away from supplements in greater and greater numbers. That would be unfortunate as many supplements provide real health benefits.

As Americans come to depend on supplements to address serious health concerns, it is all the more important that government ensure that products are safe and that claims on labels are backed by solid scientific evidence. We support S. 722 and urge Congress to go further as we have suggested.

We wish to thank the Committee for the opportunity to testify.

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[7] Food and Drug Administration Regulations on Statements Made for Dietary Supplements Concerning the Effect of the Product on the Structure or Function of the Body; Final Rule, 65 Fed. Reg. 999, 1018 (Jan. 6, 2000).

[8] General Accounting Office, *Food Safety: Improvements Needed in Overseeing the Safety of Dietary Supplements and 'Functional Foods,'* at 23 (GAO/RCED--00-156 July 2000)

[9] Chris Adams, *Splitting Hairs on Supplement Claims, Under the FDA's Guidelines, Improving Health is OK; Curing a Disease Isn't,* Wall St. J., Feb. 22, 2000, at B1.

THE DIETARY SUPPLEMENT HEALTH AND EDUCATION ACT OF 1994: IT MAKES SENSE – LET'S MAKE IT WORK

Testimony of the Council for Responsible Nutrition before the Oversight Subcommittee of the Senate Governmental Affairs Committee

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JUNE 8, 2004

Senator Voinovich and Senator Durbin, the Council for Responsible Nutrition (CRN) appreciates the opportunity to appear before this Subcommittee to discuss the status of dietary supplement regulation ten years after passage of the Dietary Supplement Health and Education Act of 1994. CRN is a trade association representing the mainstream core of the dietary supplement industry. Our members include manufacturers and marketers of national brands as well as store brands of dietary supplements available to consumers through the mass market, natural food stores, direct sales, and mail order. Our members include the companies that make the finished products as well as the companies that supply the bulk ingredients such as vitamins, minerals, fatty acids, and botanicals.

PURPOSE OF DSHEA

DSHEA was passed for two reasons: to ensure that consumers would continue to be able to choose among a wide variety of safe dietary supplements, and to increase the

information available to consumers about the uses of dietary supplements. The past 10 years have demonstrated that these purposes are being fulfilled, as are other goals established by the law.

DSHEA was made necessary because FDA had a history of attempting to unreasonably restrict the formulation of dietary supplements and because Commissioner David Kessler appeared to be harking back to the notion of imposing broad restrictions. In the 1970's, FDA had finalized regulations that would have restricted vitamin and mineral supplements to no more than 150% of the daily reference amount. This would have meant a limit of only 90 mg for vitamin C, for example. These regulations were overturned by the courts and by legislation passed in 1976 that added Section 411 (vitamins and minerals) to the Food, Drug & Cosmetic Act.

In 1993, Commissioner Kessler published an Advance Notice of Proposed Rulemaking suggesting numerous restrictions that might be placed on dietary supplements, including:

- Limiting the dosage of vitamins and minerals to low multiples of the daily reference value,
- Nor permitting the sale of dietary supplements containing amino acids, and
- Treating most herbs and botanicals as inherently therapeutic and restricting them to sale as drugs.

This set off the storm of protest that ultimately resulted in the passage of DSHEA in 1994. DSHEA specified the types of ingredients that were to be permitted in dietary supplements and has been successful in maintaining access to a broad range of products.

On the information side, FDA in 1993 and 1994 was proposing to approve health claims for antioxidant vitamins and for fiber naturally occurring in foods, but not for dietary supplements providing exactly the same beneficial ingredients. Thus, it appeared the dietary supplements were unlikely to benefit from FDA's approach to health claims under the Nutrition Labeling and Education Act, and the industry sought some additional means of conveying information to consumers. DSHEA authorized Statements of Nutritional Support, including statements describing how a product affects the structure or function of the body. Companies making such statements are required to have substantiation and to notify FDA within 30 days. This provision was self-implementing and began to be utilized soon after DSHEA was passed. In January 2000, FDA finalized extensive rules defining the scope of appropriate structure/function statements, and today more than 10,000 letters of notification have been filed with FDA regarding such claims. Companies using such statements must also include a label disclaimer saying the claim has not been evaluated by FDA, in order to distinguish these statements from approved health claims. The disclaimer also says the product is not intended to diagnose, treat, cure or prevent disease, to distinguish the statements from approved drug claims.

The ten most commonly utilized types of structure/function statements in the marketplace have to do with immune function, heart health, antioxidant effects, gastrointestinal function, healthy joints, cognitive function, men's health issues, weight loss or metabolism, energy or endurance, and women's health issues. Consumers have a vital interest in receiving more information about these topics, and DSHEA was successful in devising a means of providing that information in product labeling.

DSHEA DID NOT CHANGE THE REGULATORY STATUS OF DIETARY SUPPLEMENTS

Dietary supplements have always been considered as a subcategory of foods. This official categorization was not created by DSHEA, as some of our critics persist in asserting, but instead predates DSHEA by some 56 years. The FD&C Act of 1938 included dietary supplements within the category of foods for special dietary uses. FDA established a regulatory definition of such products in 1941, and that definition was incorporated into Section 411 of the Act by the vitamin amendments of 1976. The definition is extremely broad, covering vitamins and minerals but also all "other ingredients" intended for use in supplementing the diet.

DSHEA reconfirmed that dietary supplements were to continue to be regulated as foods and established a specific definition to clarify the categories of ingredients that were to be permitted in dietary supplements.

NEW INGREDIENTS

DSHEA "grandfathered" dietary supplement ingredients already on the market as of October 1994, in the same way the 1958 food additive amendments to the Food, Drug and Cosmetic Act "grandfathered" as safe hundreds of substances already being used in foods at the time those amendments were adopted. DSHEA established a premarket notification procedure that would be required for new ingredients used in dietary supplements in the future. Companies are now required to provide a notification to FDA regarding any new ingredient at least 75 days before marketing it, setting forth the basis for considering the ingredient to be "reasonably expected to be safe." FDA has been

receiving these notifications on a regular basis since the passage of DSHEA and has been giving them serious attention. A recent analysis by the American Herbal Products Association indicated that there have been 138 unique notifications filed, of which FDA has rejected 65, or almost half. The rejections are generally due to a company's failure to sufficiently establish the identity of the ingredient or a failure to provide sufficient information to provide a basis for concluding that the ingredient is reasonably expected to be safe.

SAFE AND BENEFICIAL DIETARY SUPPLEMENTS

Health foods and dietary supplements have been popular with the American public for at least a hundred years, and today dietary supplements are used by 70% of the population at least some of the time and by 40 to 50% of the population on a regular basis. This is just as true in Iowa and Illinois as it is in New York and California. By far the most popular single product category is the multivitamin, with or without minerals, and several highly respected medical and nutrition authorities have recommended that it would make sense for virtually everyone to take a multivitamin. The Centers for Disease Control and Prevention are supporting a national initiative to encourage all women of childbearing age to take a multivitamin in order to get enough of the B vitamin folic acid to help protect them against having a baby with a neural tube defect such as spina bifida, the leading cause of childhood disability in this country.

Vitamin and mineral products account for $7.7 billion in retail sales in the U.S. and represent 48% of sales for the entire $16.2 billion dietary supplement category. Herbs and botanicals represent 26% of sales at $4.28 billion. Specialty products account

for 15% at $2.37 billion, and sports nutrition products represent 11% of sales at $1.83 billion.

Were it not for two specific products that have been highly controversial over an extended period of time, the dietary supplement industry would be rightly recognized to have as good a safety record and as strong a benefit profile as any other food category. However, these two products -- ephedra and androstenedione – have unfortunately loomed so large as to almost characterize the industry in the minds of some. FDA is now addressing both issues aggressively. If current FDA actions are upheld, as we expect they will be, these two ingredients will no longer be an issue when the next Congress convenes in 2005, and hopefully we will be able to work together on different types of hearings -- hearings exploring the benefits of dietary supplements and the potential health care cost savings that could be realized if more people used supplements on a regular basis.

EPHEDRA

FDA issued a final regulation early this year that banned ephedra in dietary supplement products as of April 12, 2004. That rule is currently undergoing judicial review and has survived the first phase in which the court denied an injunction. This is viewed as an indication that it is likely to survive the entire process.

It is sometimes said that it took FDA ten years to take definitive action against ephedra, but this is not an accurate description of the process. From the time former Commissioner McClellan took office and decided to resolve this ongoing issue, it took the agency less than 2 years – lightning speed in terms of the regulatory process. The

earlier delays were due to false starts, wrong turns, and an unwillingness to actually use the provisions of DSHEA as Congress intended.

ANDROSTENEDIONE

Athletes have always and apparently will always seek out products and practices that have any potential whatsoever to improve performance. Sports organizations are vigilant in attempting to assure that performance is based on good nutrition, solid training, and healthy habits and not on the use of performance-enhancing products. U.S. and international sports authorities have established lists of banned substances, the use or detection of which will cause an athlete to be disqualified from competition, and these include anabolic steroids and some precursors of anabolic steroids. Androstenedione, one of those precursors, is marketed as a dietary supplement and has been blamed for the disqualification of some athletes. In order to address the issue of andro and other precursors "closer" to testosterone, CRN and the other industry trade associations are supporting Congressional legislation that will place a long list of these ingredients under the Controlled Substances Act and thus effectively remove them from the dietary supplement category. That legislation passed the House on June 3 and is expected to pass the Senate during this session. Separately, FDA has also taken action against a number of marketers of androstenedione, asserting that the ingredient is a "new dietary ingredient" for which there has been no premarket notification filed as required by DSHEA and about which there are safety concerns. Between the Congressional and FDA action, andro should be off the table as an issue of concern by the time the next Congress convenes.

ADVERSE EVENT REPORTING

In the course of the long and drawn-out controversy over ephedra, several issues have arisen that relate to the availability and interpretation of adverse event reports. Adverse event reports come to FDA from consumers, from health professionals, and from industry. For some drugs and for vaccines and medical devices, it is mandatory for companies that receive reports of serious adverse events to forward those reports to FDA. For OTC drugs subject to FDA monographs and for conventional foods and dietary supplements, companies are not subject to a mandatory reporting requirement. After one ephedra company denied having any adverse event reports and then later submitted thousands of them, there has been pressure to change the law to require companies to report adverse events – or at least serious adverse events – to FDA. If there were to be such a requirement, it would be important for it to contain at least the protections for reporting companies and for individuals that are included in the regulations applicable to other FDA-regulated categories. The legislative proposals currently on the table tend to exceed requirements applicable to pharmaceuticals and other product categories. CRN and the other trade associations are seriously considering this issue and are supporting a seminar sponsored by the University of Minnesota School of Pharmacy later this month to further explore ways of improving adverse event reporting for dietary supplements.

Another issue of importance is how adverse event reports can and should be used. FDA recognizes that the primary function of adverse event reports is to send up a signal of a potential problem that needs to be addressed. In the evaluation of adverse event reports for drugs, devices, and vaccines, it is well recognized that it is difficult and

sometimes impossible to determine whether there is a true relationship between the event reported and the product believed to be associated with it. There are well-established criteria for probing the likelihood of a true association, and it is recognized that in most cases clinical data or additional research will be needed to determine whether a given product may result in a given adverse effect. These same factors apply to the evaluation of adverse events relating to dietary supplements, and any legislation contemplated in this area must recognize these complications or at least not run roughshod over them. Some of the legislation on the table appears to assume that every adverse event is meaningful and is a true indictment of the product said to be associated with it, and this is simply not the case.

MOUNTAINS AND MOLEHILLS

The dietary supplement industry provides safe and beneficial products valued by over 150 million Americans as integral components of a healthy lifestyle. Those consumers tend to be somewhat better educated than the average consumer. Their ranks include dietitians, pharmacists, and physicians, as well as lawyers, waitresses, truck drivers, and even U.S. Senators.

The overwhelming majority of dietary supplement products are manufactured by responsible companies operating under stringent Good Manufacturing Practices and providing science-based formulations with substantiated claims. CRN considers these products and these companies to reflect the true nature of the dietary supplement industry. This true picture can be obscured when critics focus narrowly on a handful of fringe products and attempt to portray these as representative of the industry as a whole.

We are supporting FDA's efforts to deal with these fringe products, and we believe those efforts are proving effective. However, molehills are being made into mountains, and the smoke from the barrage of firepower being aimed at the fringes is obscuring and overwhelming any reasonable perception of the category as a whole. The broadside by *Consumer Reports* is an example of this lack of perspective, and CRN has described it as an effort to create a hurricane from a drop in the bucket. (See attachment.)

There are those who believe dietary supplements should be regulated like drugs. If this were the case, dietary supplements would also cost like drugs and perhaps be restricted in availability. Consumers have repeatedly spoken out in letters and calls and visits to their elected representatives, saying they want to be able to choose from a wide variety of dietary supplements for health promotion and disease prevention. CRN does not deny that some problems exist, and we have been and will continue to be working toward resolution of those problems. With any luck at all, most of those problems will be behind us when the new Congress convenes in January 2005, and we will be able to return to hearing rooms like this one to address positive questions such as the role of dietary supplements in improving the health of the population and ultimately in reducing health care costs associated with preventable conditions.

Consumer Reports: Creating a Hurricane from a Drop in the Bucket

-- CRN Response to an article in the May 2004 issue of *Consumer Reports* --

Prepared by
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STATEMENT FROM ARTICLE	CRN RESPONSE
"If you can buy it at a clean, well-lighted store, if it's 'all-natural,' it's not going to do you serious harm, right? That's what many Americans assume about dietary supplements. But while most supplements are probably fairly benign, CONSUMER REPORTS has identified a dozen that according to government warnings, adverse-event reports, and top experts are too dangerous to be on the market. Yet they are."	Most supplements are safely used by 150 million American adults each year.
"The potentially dangerous effects of most of these products have been known for more than a decade ...yet until very recently, the U.S. Food and Drug Administration had not managed to remove a single dietary supplement from the market for safety reasons."	FDA was reluctant to use the full force of regulatory authority provided under DSHEA until Dr. Mark McClellan decided to test the law's powers, saying that you cannot declare that a law doesn't work until you try to make it work. FDA's lack of interest in proving the law can work, rather than an inability under the law to take action, has been one reason that FDA has not until recently removed a single dietary supplement product from the market. The other reason is that the overwhelming majority of dietary supplements are safe.
"Despite these actions against high-profile supplements, whose dangers were so well-known that even industry trade groups had stopped defending them, the agency continues to be hamstrung by [DSHEA]."	Although ephedra had been used without harm by millions of consumers, industry trade groups chose not to challenge FDA's action, taken under DSHEA, to declare ephedra presents an "unreasonable risk." As for androstendione, FDA has declared it did not meet the 75-day notice of new ingredient as required under DSHEA and consequently is being illegally marketed as a dietary supplement. That is an action FDA could have taken at any time since DSHEA was passed and could have been taken in response to repeated questioning by Senators Harkin and Hatch as to whether androstendione was a legal dietary

CRN Response to an article in the May 2004 issue of *Consumer Reports*

	supplement. Industry supports legislation to move androstendione to a controlled substance category.
"While drug manufacturers are required to prove that their products are safe before being marketed, DSHEA makes the FDA prove that supplements on the market are *unsafe*..."	Premarket approval is not a guarantee of safety as witnessed by those drug products that have been approved by FDA, only to be later recalled due to safety concerns. Under DSHEA, FDA can immediately remove a product if it believes that product poses an imminent hazard. In addition, just because there is no premarket approval requirement it does not mean that companies don't do testing, or that the products are unsafe.
"To regulate drugs, annual sales of which are 12 times the amount of supplement sales, the FDA has almost 43 times as much money and almost 48 times as many people."	It's obvious that drugs require stronger regulation than supplements.
"The law has never been fully funded," said William Hubbard, FDA associate commissioner for policy and planning. "There's never been the resources to do all the things the law would command us to do."	At a recent congressional hearing, Robert Brackett, Ph.D., the director of CFSAN, repeatedly asserted that DSHEA provides [FDA] sufficient authority necessary to remove potentially harmful products from the market. Dr. Brackett further specifically assured the committee that FDA and HHS were not seeking additional legislation or modifications to DSHEA at this time. The law could certainly benefit from fuller implementation, something which FDA is now pursuing.
"But critics of DSHEA think the ban illustrates the extremes to which the FDA must go to outlaw a hazardous product."	DSHEA added enforcement authorities for FDA that were not previously available to the agency. Under DSHEA, FDA has two options for removing unsafe products from the market. One of those options includes immediate removal if the agency believes the product presents an "imminent hazard." While the agency would then have to make a scientific case for maintaining the ban, it is not unreasonable to expect that FDA's decision be based on sound science, rather than political rhetoric. Products should not be allowed to be removed from the market based solely on bad publicity or a precautionary principle run amok.
"Supplement-industry advocates say the ephedra ban demonstrates that DSHEA gives the FDA enough power to protect consumers from unsafe products. 'I don't think there's anything wrong except that FDA has only recently begun vigorous and active enforcement of the law,' said	Industry opposed FDA's proposed action because it was not scientifically based. More importantly, as the article correctly points out, "the General Accounting Office said the FDA 'did not establish a causal link' between taking ephedra and deaths or injuries," and the agency was forced to drop its proposal. The Cantox Report, the report

CRN Response to an article in the May 2004 issue of *Consumer Reports*

Annette Dickinson, Ph.D., president of the Council for Responsible Nutrition, a major trade association for the supplement industry...When the agency initially tried to rein in ephedra use in 1997, after receiving hundreds of reports of adverse events, it sought not an outright ban but dosage restrictions and sterner warning labels. The industry mounted a furious counter attack, including the creation of a public relations group called the Ephedra Education Council and a scientific review from a private consulting firm, commissioned by Dickinson's trade group, that concluded ephedra was safe."	commissioned by CRN, did identify conditions of safe use for ephedra, including a specific dose; and, the report also identified subsets of the population that should not use ephedra, reinforcing the label warnings that many companies had already been voluntarily adding to their product.
"...supplement manufacturers can introduce new products without any testing for safety and efficacy."	If a supplement manufacturer wants to introduce a new ingredient, it must provide FDA with 75 days notice, along with safety information. If FDA has any concerns about the ingredient or the submitted safety profile, the agency can request more information or deny the product's entry into the marketplace. Since the passage of DSHEA, there have been 138 "unique" New Dietary Ingredient notification (NDI) filings, 65 of which were rejected, indicating FDA's ability to "turn down" a product it deems questionable.
"While DSHEA gave the FDA authority to impose similar [GMP] standards on supplements, it took until 2003 for the agency to propose regulations—as yet not final—to implement that part of the law."	The industry proposed GMPs to FDA as early as 1995. Responsible companies did not wait for FDA to issue its GMP rule but instituted their own GMPs, some of which are even more stringent than those for drug companies.
"By law, drug companies are required to tell the FDA about any reports of product-related adverse events that they receive from any source. Almost every year, drugs are removed from the market based on safety risks that first surfaced in those reports."	Reporting of AERS is mandatory only for prescription drugs and some OTC products. Monographed OTC drugs and food products are not required to report AERs. CRN and other industry trade associations could support mandatory reporting of serious adverse events. That drugs are removed from the market almost every year based on AERs reinforces the fact that premarket approval is not a guarantee of safety.
"Many makers market their supplements as 'natural,' exploiting assumptions that such products can't harm you."	Many consumers want "natural" products, for a variety of reasons. However, it is insulting to consumers to assume they can be "exploited" into thinking that natural means no harm.
"But...more than two years after the import ban [on Aristolochia] went into effect, CR was able to purchase products online that were labeled as containing Aristolochia."	This is not the fault of a law ... it is the fault of companies engaging in illegal marketing.

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"Do not take daily doses of vitamins and minerals that exceed the safe upper limits…it's possible to overdose on some of them [vitamins and minerals].	CRN agrees that safety limits should be observed. CRN's scientist, John Hathcock, Ph.D., is regarded worldwide as an expert in the field of vitamin and mineral safety. His CRN publication, *Vitamin and Mineral Safety*, soon to be published in its second edition, is a resource for regulators, government, scientists and industry. While it is possible to overdose on vitamins and minerals, inadequate intakes are a more common problem.
"Stay away from supplements for weight control."	With obesity such a huge problem in this country, it is irresponsible to suggest that consumers should not have the choice of taking any weight control supplements. However, as with all products, consumers should pay close attention to labeling advice and not exceed the dose. In addition, any weight management products should be used in conjunction with healthy lifestyle choices, not as substitutes for proper eating habits and regular exercise.

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ASPET Position Statement on Dietary Supplement Regulation
June 1, 2004

The American Society for Pharmacology and Experimental Therapeutics (ASPET) supports re-evaluation of regulations and legislation that currently excludes dietary supplements from regulation under the Federal Food, Drug, and Cosmetic Act. ASPET believes it is timely to establish labeling, advertising requirements, and restriction of sales of dietary supplements that may prove harmful to consumers. ASPET also supports regulation and legislation requiring manufacturers of dietary supplements to promptly inform the Food and Drug Administration of any reports of adverse experiences with the use of these supplements. ASPET commends the April 2004 FDA rule prohibiting the sales of dietary supplements containing ephedrine alkaloids. The FDA rule underscores the potential for abuse of other unregulated substances, including those containing anabolic steroids or other products containing potent pharmacologic agents that may result in adverse reactions or death of consumers, including significant numbers of the juvenile population.

The available scientific evidence suggests strongly that the unregulated marketing and use of some dietary supplement products may present a significant and unreasonable risk of illness, injury, or even death under ordinary conditions of use or even when used as recommended or suggested in the labeling of these products. Legislation addressing truth in labeling, advertising, and sales of these products will help, but may not alone be sufficient to address this serious public health issue. In addition, legislation requiring the reporting of adverse experiences with the use of these supplements will assist in the identification of issues involving the chemistry, manufacturing, and control of these products.

Surveys confirm that the majority of U.S. consumers mistakenly believe that herbal products and dietary supplements are regulated by the FDA and have been scientifically proven to be safe and effective, and to contain the ingredients and their amounts stated in product packaging. The unregulated use of dietary supplements provides an additional risk magnified by the lack of analytical oversight and control in manufacturing practices. Sound pharmacological studies are needed to help determine the potential for interactions among herbal products, dietary supplements, and prescription drugs as well as adverse effects on chronic disease processes.

Some dietary supplements and botanical products exhibit drug-like properties because they contain drugs, even though they are natural products. Genuine, effective regulatory and legislative action is needed to help to remedy an important public health problem created by the unregulated use of products whose efficacy is unproven and whose manufacturing standards are unregulated. It is the position of ASPET that a congressional review of the 1994 Dietary Supplement Health and Education Act (DSHEA) is timely and warranted.

ASPET is a 4,800 member scientific society whose members conduct basic and clinical pharmacological research in academia, industry and the government. Our members research efforts help to develop new medicines and therapeutic agents to fight existing and emerging diseases.