

Department of Health and Human Services

**OFFICE OF
INSPECTOR GENERAL**

**Adverse Event Reporting
For Dietary Supplements**

An Inadequate Safety Valve



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EXECUTIVE SUMMARY

PURPOSE

To assess the effectiveness of the Food and Drug Administration's (FDA) adverse event reporting system for dietary supplements in protecting the American consumer.

BACKGROUND

Dietary supplements are increasingly popular. Currently about 60 percent of Americans take some form of dietary supplement every day without any apparent problems. Supplements include substances such as vitamins, minerals, botanicals, and amino acids. Although many of these supplements can be beneficial, there are risks associated with some. For example, ginkgo biloba may lead to excessive bleeding, vitamin A in high dosages during pregnancy may lead to birth defects, and St. John's Wort may reduce the effectiveness of some antiviral drugs. Unlike new prescription and over-the-counter drugs, FDA does not have the authority to require supplements to undergo premarket approval for safety and efficacy. Instead, it relies mostly on its adverse event reporting system to identify safety problems.

FDA's Adverse Event Reporting System for Dietary Supplements

FDA's adverse event reporting system for dietary supplements includes (1) detecting adverse events, (2) generating signals of possible public health concerns, (3) assessing those signals, and (4) taking appropriate safety actions based on its assessment. An adverse event is an incident of illness or injury that *may* be associated with a product or ingredient. With further investigation, the association may or may not be confirmed. Reporting adverse events is entirely voluntary, and FDA receives reports from a variety of sources including consumers and health professionals.

When a signal of a possible health problem is generated from the adverse event reporting system, FDA assesses whether it is an actual public health problem warranting attention. FDA can assess these signals by reviewing scientific literature, consulting with experts, reviewing clinical data, conducting its own laboratory tests, and/or commissioning studies. If FDA confirms that a public health problem exists it can take a range of safety actions, such as issuing warnings to consumers and health professionals, issuing import alerts, requesting product recalls, or seizing products.

This Inquiry

In this report, we evaluate how well FDA's adverse event reporting system for dietary supplements functions as a consumer protection tool. We analyzed data from FDA's database; reviewed FDA laws, regulations, policies, and procedures; reviewed several adverse event reports; reviewed relevant literature; and interviewed FDA officials, industry representatives, and scientific experts. We did not evaluate the internal

operating procedures of the system.

FINDINGS

FDA's adverse event reporting system detects relatively few adverse events.

Adverse event reporting systems typically detect only a small proportion of the events that actually occur. This appears to be especially true of FDA's system for dietary supplements. A recent FDA-commissioned study estimated that FDA receives less than 1 percent of all adverse events associated with dietary supplements. Among the factors that may contribute to under-reporting are that many consumers presume supplements to be safe, use these products without the supervision of a health care professional, and may be unaware that FDA regulates them. FDA's limited outreach concerning this system contributes to this unawareness.

It has difficulty generating signals of possible public health concerns.

FDA lacks much of the information that is necessary to effectively analyze adverse event reports and to generate possible signals of concern. Below we document the lack of information by presenting FDA data between 1994-1999.

Limited medical information. FDA did not receive the medical records for 58 percent (464 of 801) of the reports for which it requested them. Only 20 percent (527 of 2,547) of adverse events reports received by FDA came from health professionals.

Limited product information. FDA was unable to determine the ingredients for 32 percent (1,153 of 3,574) of the products mentioned in adverse event reports. FDA does not have the product labels for 77 percent (2,752 of 3,574) of the products mentioned in reports. FDA does not have product samples for 69 percent (130 of 188) of the products for which it requested them. Product samples are especially helpful because dietary supplement ingredients are not standardized.

Limited manufacturer information. FDA reports that it has received fewer than 10 adverse event reports directly from manufacturers. FDA was unable to determine the manufacturer of dietary supplement products for 32 percent (1,153 of 3,574) of the products involved in reports. FDA was unable to determine the city and State for 71 percent (644 of 904) of the manufacturers.

Limited information on the dietary supplement consumer. FDA was unable to follow-up with 27 percent (214 of 801) of the reports it tagged for follow-up primarily because the reports lacked sufficient information to identify the alleged injured party.

Limited ability to analyze trends. FDA has difficulty analyzing trends of adverse event reports because it lacks an adequate computer database for routine analysis and receives relatively few reports.

FDA lacks vital information to adequately assess signals of possible public health concerns generated by the adverse event reporting system.

In order to assess such signals, FDA must draw upon key information external to the system. But FDA faces obstacles in obtaining such information. For a recent case study that documents these obstacles see appendix A.

Limited clinical information. There is some clinical information available on dietary supplements and more is becoming available every day. But, the current regulatory framework for dietary supplements permits manufacturers to market a supplement without premarket safety studies. For this and other reasons, FDA has relatively little clinical information on particular products. The law requires manufacturers of certain new dietary ingredients to notify FDA 75 days prior to market and include “relevant” safety information. However, very few dietary ingredients are subject to this requirement, and FDA has issued no guidance on the type of safety information that should be submitted.

Limited information on consumer use. FDA lacks a mechanism to track the number of consumers using a particular supplement. Such information can be helpful to determine the incidence of certain adverse events in the user population and thus, the extent of the public health problem that it poses.

As a result, FDA rarely takes safety actions related to the adverse event reporting system.

Safety actions can be of significant benefit to consumer safety. For example, based on FDA’s investigation of adverse event reports, it found products containing plantain were contaminated with *Digitalis lanata*, a plant that can cause heart attacks in certain individuals. FDA issued a consumer warning against certain products containing plantain and asked supplement manufacturers to voluntarily recall their products contaminated with *Digitalis lanata*.

But, between January 1994 and June 2000, we were able to document only 32 safety actions that FDA took based on the adverse event reporting system—a period when more than 100 million people were taking supplements. With limited information to draw upon to generate and assess signals, FDA rarely reaches the point of knowing whether taking a safety action is warranted.

Public disclosure of adverse event reports can also be considered a type of safety action. FDA uses its website as its main vehicle for disclosure. However, its website has significant limitations; for example, it provides no evaluation of the reports, contains misleading information, and is rarely updated.

RECOMMENDATIONS

Our evaluation of FDA’s dietary supplement adverse event reporting system leads us to conclude that without further development of the overall regulatory framework for

dietary supplements, the potential of the system to serve as a consumer safeguard is inherently limited. The program simply cannot serve as an adequate safety valve until other measures are taken that will allow FDA to generate and confirm signals of possible public health concerns.

Below we offer our recommendations as a blueprint for actions that FDA can take over a reasonable period of time. It has already called for some of them in its strategic plan for dietary supplements. We recognize that some of our recommendations will call for legislative or regulatory changes. We also recognize that resources are limited and that some of our recommendations may require additional resources.

RECOMMENDATION 1: Facilitate greater detection of adverse events.

Require dietary supplement manufacturers to report serious adverse events to FDA for some products. FDA should examine what types of products or ingredients should fall under this requirement. FDA already requires pharmaceutical manufacturers to report adverse events for all prescription and some over-the-counter drugs.

Contract with Poison Control Centers to obtain their adverse event reports on dietary supplements. These centers hold information that may be useful to FDA. Reports from Poison Control Centers may provide additional data to help generate signals of possible public health concern.

Inform health professionals and consumers about the adverse event reporting system for dietary supplements. The main way FDA can accomplish this is by expanding its outreach to health professionals and including information about the safety actions it has taken. Other possibilities include requiring manufacturers to provide a toll-free number on their product labels or placing FDA's toll-free number on labels.

RECOMMENDATION 2: Obtain more information on adverse event reports in order to generate stronger signals of public health concerns.

Educate health professionals about the importance of including medical information in adverse event reports. Without medical information about the alleged injured parties, FDA lacks crucial information for determining the likelihood that an adverse event was related to the use of a dietary supplement. When FDA conducts outreach it should encourage health professionals to obtain permission from their patients to release their medical records when appropriate.

Require dietary supplement manufacturers to register their products with FDA. A complete product registry would allow FDA to instantly access a list of all of the ingredients in a particular product and determine the product manufacturer's name as soon as it receives an adverse event report.

Require dietary supplement manufacturers to register with FDA. A registry of manufacturers would enable FDA to quickly and easily contact a manufacturer whose product was associated with an adverse event to obtain additional information.

Notify manufacturers when FDA receives a serious adverse event report. Alerting manufacturers of adverse events in which their products have been mentioned would give FDA the opportunity to obtain more product information from the manufacturer. It would also allow manufacturers to reevaluate the safety profile of the product, including manufacturing procedures, in a timely manner.

Emphasize to health professionals and consumers the importance of providing a way to identify the alleged injured party. Without this information FDA may be unable to gather additional information excluded from the report.

Develop a new computer database to track and analyze adverse event reports. To help identify signals, FDA needs a database that allows for querying by ingredients as well as products and types of adverse events.

RECOMMENDATION 3: Obtain vital information to adequately assess signals generated by the adverse event reporting system.

Issue guidance on the type of safety information that manufacturers should include in the 75-day premarket notification requirement for some new dietary supplement ingredients. FDA should take full advantage of its existing authority to obtain as much safety information as possible prior to marketing.

Explore the possibility of a monograph system for dietary supplements that would contain safety information on particular ingredients. Monographs are point papers on particular ingredients that contain safety and efficacy information. Such a system would allow FDA to have in a systematic fashion safety information that it could rely upon to help make decisions.

Collaborate with the National Institutes of Health in setting a research agenda addressing safety issues. Another way that FDA can gain clinical information is by collaborating with the National Institutes of Health that funds and conducts research related to dietary supplements.

Assist industry and the United State Pharmacopeia in standardizing dietary supplement ingredients, particularly botanicals. Standardized ingredients would allow FDA to have the confidence that in taking action against unsafe products or ingredients it is addressing all the products posing a health risk.

Expedite the development and implementation of good manufacturing practices for dietary supplement manufacturers. Standardized ingredients must be complemented by FDA enforcing those standards through good manufacturing practices. These are essential for FDA to be assured of the precise contents of each batch of supplements that is manufactured.

RECOMMENDATION 4: Disclose more useful information to the public about dietary supplement adverse events.

FDA should provide more useful data on its website so that consumers can, to some extent, evaluate the likelihood that the adverse event was related to the supplement. FDA could update the information on its website more regularly. FDA could also accomplish this by providing summary data on the numbers and types of reports received by product types or ingredients. Over time, as resources become available it could consider indicating the likelihood the event was caused by a product.

COMMENTS

We received comments on our draft reports from the Food and Drug Administration. We also solicited and received comments from three trade associations (Consumer Healthcare Products Association, American Herbal Products Association, and the Council for Responsible Nutrition) and two public interest organizations (Public Citizen's Health Research Group and the Center for Science in the Public Interest.) See appendix C for the comments in their entirety.

On the basis of these comments we made several changes that are reflected in this final report. Some involved minor technical changes, and others involved brief elaborations to clarify and add context. In two instances we modified our recommendations to target them more effectively and to minimize regulatory burden. We limited the scope of mandatory reporting of adverse event reports to events that are both serious in nature and fall under a certain subset of products to be determined by FDA. Similarly, instead of calling for FDA to notify manufacturers of all adverse event reports it receives, we called for it to notify the manufacturers of serious reports only.

Food and Drug Administration

FDA reported that our findings were a fair assessment of the challenges it faces. It also agreed with the majority of our recommendations. As part of its comments, it categorized our recommendations into three areas: (1) tasks that it can currently accomplish, (2) tasks that require additional resources, and (3) tasks that require both legislative changes and additional resources. FDA documented the progress it has made in each of these categories. FDA indicated that the major difficulty it faces to improving the system is a lack of adequate resources.

FDA is making progress toward improving the system along the lines we call for in our report. Many of our recommendations are already included among FDA's top priorities for the year as well as in its 10-year strategic plan. We also encourage FDA to seek the authority it needs to require manufacturer and product registration and mandatory manufacturer reporting of adverse events.

Trade Associations

The three trade associations provided some support for our recommendations, but for the most part, they were highly critical of both our findings and recommendations. While we disagree with the thrust of their comments, they help sharpen the issues that need to be addressed as part of any reform.

One of their major critiques was that we chose not to evaluate the internal operating procedures of FDA's adverse event reporting system, thereby leaving us with little basis for our broader recommendations. We agree that there could be value to a procedural review. FDA should be doing everything it can to make sure the current system operates as effectively as it possibly can. However, we offer strong evidence that the current system is fundamentally flawed and cannot provide an adequate consumer safeguard unless FDA is given more tools to do the job.

Another significant critique was that we failed to view dietary supplements in the context of a food-related system. This failure, they claim, led us to call for more extensive oversight, similar to that for prescription drugs. Our inquiry focused on how the current system was functioning and made us acutely aware of just how little information FDA has available to determine whether adverse events about dietary supplements (however characterized) present danger signs that should be addressed. Without an improved capacity to obtain such information, FDA's adverse event reporting system will continue to fall short of its potential.

Still another critique was that our report reflects a negative view of dietary supplements and fails to recognize their role as self-care products that so many consumers value. We regret any implication of such a negative view. If the kind of recommendations we call for are enacted, we suggest that consumers would have more extensive and useful information available to them on these self-care products and could have more confidence that an adverse event reporting system was providing them with a valuable measure of protection.

Public Interest Organizations

The two public interest organizations strongly supported our report. Their main critique was that we did not go far enough. One called for legislative changes that, over time, would significantly enhance FDA authorities. The other called for FDA to support a systematic study of dietary supplement safety and efficacy. While our evidence did not allow us to go as far as these organizations would like, it did lead us to emphasize that a comprehensive set of changes must be carried out if the adverse event reporting system is to provide an adequate consumer safety valve.

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INTRODUCTION

PURPOSE

To assess the effectiveness of the Food and Drug Administration's (FDA) adverse event reporting system for dietary supplements in protecting the American consumer.

BACKGROUND

Dietary supplements are increasingly popular. Currently about 60 percent of Americans take some form of dietary supplement every day without any apparent problems. Dietary supplements include products such as vitamins, minerals, botanicals (herbal products), and amino acids.¹ Healthy consumers use supplements to increase their energy, boost their immune systems, prevent memory loss, build muscle mass, or lose weight. Ill people turn to supplements as an alternative to traditional treatments, to complement prescription drugs, to save money needed to buy more expensive prescription drugs, or in general to promote good health. Research studies suggest some products are beneficial. For example, glucosamine and chondroitin may relieve symptoms of osteoarthritis.² Saw palmetto may improve the symptoms for men with benign prostatic hyperplasia.³ Folic acid may reduce the risk of neural tube defects in newborns.⁴

Although many of these supplements can be beneficial, risks are associated with some. For example, ginkgo biloba may lead to excessive bleeding, high dosages of vitamin A during pregnancy may lead to birth defects, and St. John's Wort may compromise the effectiveness of some antiviral drugs. Unlike new prescription and over-the-counter drugs, the law does not require supplements to undergo premarket approval for safety and efficacy. Instead, FDA relies mainly on its adverse event reporting system to identify safety problems.

FDA's Adverse Event System for Dietary Supplements

In 1993 FDA created a system to collect and review adverse event reports on supplements. An adverse event is an incident of illness or injury that *may* be associated with a product or ingredient. FDA's adverse event reporting system for dietary supplements includes (1) detecting adverse events, (2) generating signals of possible public health concerns, (3) assessing those signals, and (4) taking appropriate safety actions based on its assessment. The system for dietary supplements, according to the director of the Center for Food Safety and Applied Nutrition, "provides an essential monitoring tool for identifying potential serious public health issues that may be associated with the use of a particular product or type of product already in the marketplace that needs to be investigated and critically evaluated."⁵

Reporting adverse events associated with dietary supplements to FDA is entirely voluntary. FDA receives adverse event reports on dietary supplements from consumers, health professionals, and manufacturers through a variety of sources, including State

health departments, Poison Control Centers, direct communication with individuals, and MedWatch, a computerized reporting system used to monitor a variety of FDA-regulated products. Reported events range in severity from nausea and dizziness to cardiac arrest or death.

FDA relies on the adverse event reporting system to generate signals of possible public health concerns. When signals are generated, FDA still needs to assess the signal to determine if a public health problem exists. FDA can investigate the signal in many ways including examining clinical information and/or conducting laboratory tests. If the signal is confirmed, FDA can take a variety of actions to protect the public depending on the seriousness of the problem. FDA safety actions range from issuing warnings to consumers and health professionals to seizing products. FDA can also take civil and enforcement actions. (See the Primer on page 4 for additional information on the system.)

Dietary Supplement Health and Education Act

In 1994, Congress passed the Dietary Supplement Health and Education Act based on the premise that “legislative action that protects the right of access of consumers to safe dietary supplements is necessary to promote wellness.”⁶ The Act defined the term “dietary supplement” and legitimized it as a category of health care products. It also created a new regulatory framework for dietary supplements while assuring consumers broad access.

The Act generally classifies dietary supplements as a category of food. As such, they fall under the authority of the FDA, in its Center for Food Safety and Applied Nutrition. FDA has authority for dietary supplements for (1) product safety, (2) product labeling including claims, (3) notification of new dietary ingredients, and (4) good manufacturing practices. FDA has issued over 25 Federal Register notices regarding dietary supplements, mostly focused on labeling and product claims. Although the Act is grounded on the presumption that dietary supplements are safe, it does provide FDA with the authority to take action against a dietary supplement or ingredient that “presents a significant or unreasonable risk of illness or injury.”⁷

Our Inquiry

FDA’s adverse event reporting system for dietary supplements is a particularly important safety valve for consumers due to the lack of other complementary oversight systems, such as premarket approval, and the increased popularity of dietary supplements. In this report, we examine how well the system (1) detects adverse events, (2) generates signals of public health concerns, (3) assesses these signals, and when necessary, (4) takes appropriate actions to protect consumers. We do not evaluate the safety of dietary supplements themselves, nor do we evaluate the adequacy of other FDA activities related to dietary supplements, such as labeling requirements and product claims.⁸ Finally, we do not evaluate the internal operating procedures of the system.

We analyzed data from FDA; reviewed FDA laws, regulations, policies, and procedures; reviewed several adverse event reports; examined the product labels and claims for 30 dietary supplements; reviewed relevant literature; and interviewed relevant FDA officials, industry representatives, and scientific experts.

We conducted this inspection in accordance with the *Quality Standards for Inspections* issued by the President's Council on Integrity and Efficiency.

PRIMER ON FDA'S ADVERSE EVENT REPORTING SYSTEM

DETECTING ADVERSE EVENTS

- D FDA receives adverse event reports through a variety of reporting mechanisms: MedWatch, Poison Control Centers, FDA District Offices, State Health Departments, and direct contact with individuals.
- D Consumers, health professionals, and manufacturers are the three categories of reporters.

GENERATING SIGNALS OF POSSIBLE PUBLIC HEALTH CONCERN

- D FDA enters the adverse event report into its database and forwards it to its clinical staff for review.
- D FDA determines if follow-up to the report is needed to obtain more information based on whether FDA considers the event to be a "high concern," "serious," or "clinically significant."⁹ If FDA does not request follow-up, it closes the file. In either case, FDA maintains the report in the database to be used for later analysis.
- D When FDA requests follow-up of an individual report, it may request one or more of the following: product label, product sample, consumer's medical records, and information about how much was consumed and for how long.
- D The following criteria must be met for follow-up: adequate contact information of the reporter must exist, and the injured party must be identified in some way.
- D After follow-up, FDA reviews the information collected and determines whether it has enough information to evaluate the report. If it does, FDA makes an evaluation and closes the file. FDA maintains the report in a database. If FDA lacks enough information it may request information again. In cases where FDA cannot obtain the information the file is closed.
- D Adverse event reports in and of themselves do not lead to conclusive assessments of the safety of a product or ingredient. Rather, FDA uses adverse event reports to generate signals of possible public health concerns. Signals are most often generated when FDA identifies a trend, although one well-documented report may be enough to create a signal.

ASSESSING SIGNALS

- D FDA relies on its own evaluation as well as outside sources such as medical literature, clinical studies, and expert advisors to evaluate whether the signal signifies a public health problem warranting FDA action.
- D FDA may also conduct its own laboratory testing of product samples to help assess and confirm signals.

TAKING SAFETY ACTIONS

- D Once FDA has confirmed a signal, it can take a variety of actions to protect the public from risks associated with dietary supplements. These actions vary depending on the seriousness of the situation. FDA can issue warnings to consumers or health professionals, require more information on product labels, request a recall of the product, or seize the product.
- D Depending on the action chosen, FDA may have to demonstrate that the product is adulterated, misbranded, or an unapproved new drug.
- D FDA also publicly discloses some elements of its database on its public website.

IMPORTANCE OF THE SYSTEM

Adverse event systems are typically used as ancillary risk identification systems. Below we present several reasons specific to dietary supplements that underscore the need for FDA's system.

Unique Role of the Adverse Event Reporting System for Dietary Supplements

Adverse event reports in and of themselves typically cannot generate conclusive evidence about the safety of a product or ingredient. Rather, the system can generate signals of possible public health problems. FDA typically uncovers signals by analyzing trends of the reports, although one well-documented report can generate a signal as well. FDA must assess these signals to confirm if in fact a public health problem exists related to a product or an ingredient. In assessing a signal, it relies on a variety of sources, such as clinical research, scientific literature, and/or laboratory testing.

In the case of dietary supplements, FDA has relatively little clinical data on ingredients and products. Thus, FDA is inherently limited in its ability to investigate signals of public health problems generated by the system. In contrast, manufacturers of new prescription drugs and over-the-counter drugs are required to submit safety data to FDA on their products prior to market (see table on the following page).

Furthermore, unlike manufacturers of new prescription and over-the-counter drugs who shoulder the burden of demonstrating the safety of their products prior to market, the burden is placed on FDA to prove that the supplement is unsafe or adulterated after the product is already on the market. And in some cases similar to other FDA products, FDA may have to prove that the product is unsafe when used as recommended by the manufacturer or suggested in the labeling; if the consumer suffers an adverse reaction after using a higher dosage than recommended or suggested in the labeling, the supplement may still be considered safe.¹⁰

The law requires supplement manufacturers to notify FDA 75 days prior to marketing new dietary supplement ingredients. However, this mechanism is only minimally effective at protecting consumers because so few ingredients are subject to this requirement. The law defines a "new" dietary ingredient as a substance that was not "present in the food supply as an article of food in a form in which the food has not been chemically altered" in the United States before October 15, 1994.¹¹ But, because FDA lacks documentation as to which dietary ingredients were marketed before 1994 and because there is a wide range of articles used for food, it is difficult for FDA to determine whether a dietary ingredient is subject to the 75-day notice requirement. To date, FDA has received 97 premarket notifications, covering 114 ingredients, 102 of which were new dietary ingredients (the remaining products/ingredients were found to be drugs or biologics).

Even when FDA receives a 75-day notification, FDA may disagree with the manufacturer's assertion with respect to the safety of the ingredient, but FDA bears the

burden of showing that the data are inadequate to provide reasonable assurance that the ingredient does not present a significant or unreasonable risk of illness if an enforcement action becomes necessary.¹²

A Comparison of FDA's Regulatory Mechanisms to Help Ensure the Safety of Products							
Product Class	Product Registration	Manufac. Registration	Premarket Approval of Products	Specific Good Manufac. Practices	Voluntary Postmarket Adverse Event Reporting System	Mandatory Manufac. Reporting of Adverse Event Reporting	Safety-Related Labeling Requirements
Dietary Supplement				under development	✓		some
Conventional Foods				✓	✓*		some
Food Additive			✓	✓	✓	some	✓
Monograph Drugs**	✓	✓		✓	✓		✓
New Drug Application Drugs***	✓	✓	✓	✓	✓	✓	✓
Infant Formula	✓	✓		proposed in 1996	✓	✓	✓
*FDA does not collect or evaluate all adverse events on all conventional food. Excluded in this system are the investigations FDA conducts following food-borne illness outbreaks. **Monograph drugs are typically over-the-counter drugs that must adhere to specific safety standards set out for each ingredient and do not undergo clinical testing. ***NDA is a new drug application that all prescription drugs and some over-the-counter drugs must submit to FDA prior to market. This application must include data that demonstrates the safety and efficacy of the product.							

Popularity of Dietary Supplements

Since the early 1990s, consumer demand for supplements has sky-rocketed. Estimated sales of dietary supplements increased nearly 100 percent between 1992 and 1996, from \$3.7 billion to \$6.5 billion.¹³ In 1999, the industry grossed an estimated \$15.4 billion.¹⁴ Today, dietary supplements are widely available in grocery stores, retail pharmacies, health food stores, and on the Internet. According to a study commissioned by FDA, over 1,500 manufacturers produce dietary supplements.¹⁵

Currently, over 60 percent of the American population uses some form of dietary supplement every day.¹⁶ Vitamin and mineral supplements are the most commonly used.¹⁷ An estimated 22.8 million consumers use herbal products in lieu of prescription medicine and 30 million use herbal products instead of over-the-counter drugs.¹⁸ The elderly are one of the largest consumer populations.¹⁹ In the words of the FDA

commissioner, “A small but disturbing number of these products have a potential for harm or bear unsupported claims. In this context, a rapidly expanding industry and a changing demographic of consumers eager to manage their own health care needs provide a significant regulatory challenge.”²⁰

Associated Risks With Some Dietary Supplements

Many consumers use dietary supplements without apparent problems. However, risks do exist. In a recent survey, 12 percent of consumers of herbal products reported that they had experienced side effects.²¹ Possible health problems associated with dietary supplements fall into three major categories: direct toxicity, interactions with other drugs or supplements, and contamination of products. Below we describe some recent study findings.

Direct Toxicity. Several clinical studies have identified serious side effects with dietary supplements. For example, high dosages of vitamin A taken during pregnancy are associated with higher rates of cranial neural crest birth defects.²² Ginkgo biloba, a popular supplement taken to enhance memory, has been found to be a blood thinner. It can lead to excessive bleeding and, in some cases, stroke.²³

Supplement-Drug Interactions. A recent survey found that about 31 percent of respondents reported taking herbal products in conjunction with prescription drugs and 30 percent took supplements with over-the-counter drugs.²⁴ Several recent studies have identified potentially dangerous interactions between drugs and herbs that can include synergistic effects, poisoning, or inactivation of one of the substances. In one recent study, researchers at the National Institutes of Health demonstrated that St. John’s Wort, typically used to enhance mood, could significantly compromise the effectiveness of antiviral drugs often prescribed to treat HIV infection.²⁵

Contamination of Products. In 1989, FDA requested an urgent recall of products containing L-tryptophan, most often used as an aid for sleep. The use of L-tryptophan was associated with an elevation of eosinophils, a particular type of white blood cell, and severe muscle pain, a syndrome referred to as the eosinophilia-myalgia syndrome. These products were associated with over 1,500 cases of adverse events reported to the Center for Disease Control and Prevention. In 1997, FDA found that certain dietary supplement products were contaminated with *Digitalis lanata*, a plant that contains powerful heart stimulants and under certain circumstances may lead to cardiac arrest.²⁶ The California Department of Health reported that 32 percent of 260 Asian herbal products selected off the shelves of California retail stores were contaminated with lead, arsenic, or undeclared pharmaceuticals.²⁷ Several reports have identified herbal products containing prescription drugs used to treat diabetes.²⁸ In another case, a large supplement manufacturer was found guilty of defrauding the government by adding synthetic ingredients to a product labeled “all natural” and thus, misbranding the product.²⁹

Concerns About Dietary Supplement Product Labels

The law prevents manufacturers from marketing dietary supplement products with labeling that is false or misleading. Labeling that omits a material fact is considered misleading under the law. Many products that lack warnings may be misbranded under this provision, and FDA may not be adequately enforcing this requirement. For example, we purchased three different brands of ginkgo biloba, a supplement that can act as an anticoagulant. Product A had no warning. Product B warned, “if you are using MAO inhibitors consult your healthcare practitioner prior to using this product.” Product C warned, “if you are pregnant or breast-feeding, taking blood-thinning medications or regularly taking aspirin, consult your health care professional before using this product.” Some industry groups have established standard warnings for certain products, but manufacturers’ use of these standard warnings is voluntary. FDA has issued a regulation requiring a warning label on dietary supplement that contain iron, but otherwise generally has not prescribed warnings or listings of side effects for particular ingredients or products.

Even when consumers are aware of the risks associated with certain dietary supplement ingredients, the ingredients or the active constituent can be listed under a variety of names that may be unfamiliar to the consumer. For example, products containing ephedrine alkaloids, a category of ingredients that act as stimulants, have several names. In our review of botanical literature we found 25 common names for botanicals containing ephedrine alkaloids including Ma Huang, Ephedra, Chinese joint-fir, Country Mallow, and Brigham’s Tea.³⁰ FDA labeling regulations for dietary supplements require that ingredients be listed under their Latin binomial names except when they are available in the *Herbs of Commerce*.³¹ FDA requires that manufacturers use common names consistent with the names standardized in the *Herbs of Commerce* to help limit the number of common names in use. However, even the *Herbs of Commerce* contains multiple common names for plants that contain ephedrine alkaloids.³²

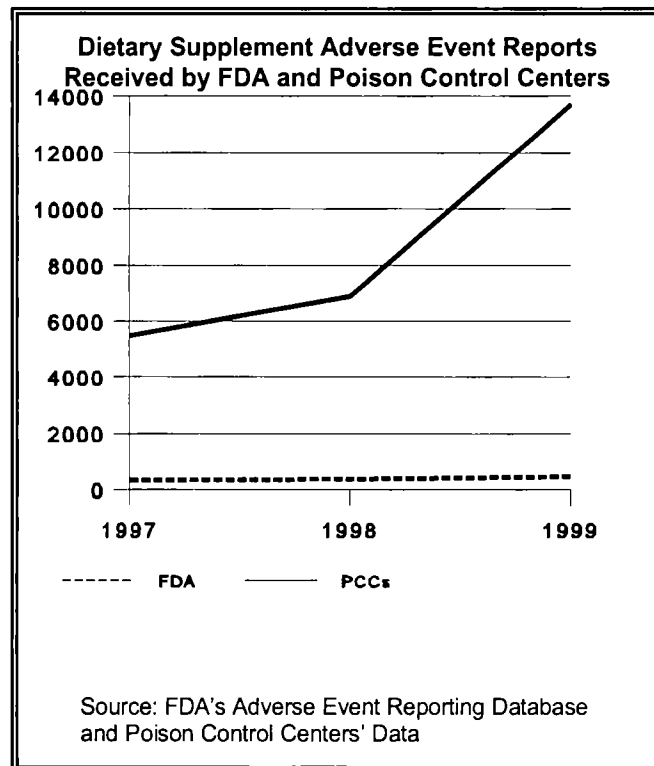
FINDINGS

FDA's Adverse Event Reporting System Detects Relatively Few Adverse Events.

Adverse event systems typically detect only a small proportion of events that actually occur. They are passive systems that depend on someone linking an adverse event with the use of a product and then reporting that event. FDA's adverse event reporting system for dietary supplements is no exception. A recent study commissioned by FDA estimated that the adverse event reports FDA receives represent less than 1 percent of all of the adverse events associated with dietary supplements.³³ We found that FDA's dietary supplement adverse event system received 2,547 adverse event reports related to supplements from 1994 through 1999—a period when more than 100 million people were taking supplements. A survey found that 12 percent (11.9 million) of all consumers using herbal products reported that they have experienced side effects or adverse reactions.³⁴

Comparison to other adverse event reporting systems. We recognize that no clear standard exists on how many reports FDA should receive. While not directly comparable, other systems appear to be receiving more reports. Most notably, Poison Control Centers—a network of sites, predominantly hospitals and academic health

centers, that respond to consumer calls about problems with products—received significantly more dietary supplement adverse event reports than FDA for the past several years. For example, in 1999 these Centers received 13,000 reports related to dietary supplements while FDA received 460 reports (see figure).^{35,36} Similarly, since 1993, the Texas State Department of Health has received 1,400 reports involving dietary supplements; thus, a single State received more than half the number of reports that FDA received during that same time period.³⁷



Manufacturers also have information on adverse events that they do not share with FDA. Dietary supplements manufacturers are not legally required to report adverse events. In one legal proceeding, the manufacturer initially reported that it had no adverse event reports, but later released hundreds of “refund requests” that detailed many adverse events.³⁸

Certain characteristics of dietary supplements may contribute to under-reporting.

Dietary supplements include natural ingredients and are self-care products. These two factors may minimize a consumer’s readiness to link an adverse event with a dietary supplement product—the first step in the reporting process.

Presumed safety. The presumed safety of dietary supplements may limit consumers’ inclination to link an adverse event with a supplement product. Many consumers believe that, due to the natural ingredients contained in dietary supplements, the products are inherently safe. Congress, in establishing the current dietary supplement regulatory system, stated, “dietary supplements are safe within a broad range of intake, and safety problems with the supplements are relatively rare.”³⁹

Self-Care products. Another factor that may contribute to under-reporting of supplement adverse events is that they are self-care products. In some instances, consumers may turn to supplements instead of over-the-counter medications, despite the fact that most dietary supplements are intended to “supplement the diet” and cannot explicitly claim to affect disease.⁴⁰ Consumers often use supplements without guidance from, or even the knowledge of, their physicians. Health professionals are often unaware that their patients are taking dietary supplements. They may not ask their patients whether they are taking a supplement and even when they do, patients may fail to inform them. A recent study found that 7 in 10 surgery patients who were taking herbal supplements failed to tell their doctors when asked.⁴¹ Thus, health professionals may be unable to link a patient’s adverse event, should one arise, with supplement use.

Perceived lack of Federal involvement. Another potential cause of under-reporting to FDA’s dietary supplement adverse event system is that the required disclaimer for specific types of dietary supplement claims permitted without prior authorization may be misinterpreted to mean that FDA has no oversight over dietary supplements. The required disclaimer, following a product’s claim states, “this statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure or prevent any disease.” In fact a recent survey showed that 50 percent of Americans think the Federal government does not regulate supplements and 16 percent were uncertain.⁴² Therefore, consumers may not think that FDA is the appropriate body to which to report.

FDA conducts little outreach. While FDA does provide information on adverse event reporting for dietary supplements on its website, many consumers may be unaware of this. FDA has not conducted targeted outreach to health care professionals encouraging physicians and alternative health care providers to ask questions about supplements, nor

has it conducted public awareness campaigns where consumers purchase supplements. In recent years, FDA has made broad efforts to inform health professionals about reporting adverse events associated with FDA-regulated products through its Medwatch system but this had done little to help counteract under-reporting of dietary supplement adverse events.

FDA's Adverse Event Reporting System Has Difficulty Generating Signals of Possible Public Health Concerns.

FDA's adverse event reporting system for dietary supplements generates signals of possible public health risks. As is the case for any database, if the data coming in are poor the analysis coming out will also be poor. Below we present the key types of information that a system needs in order to generate strong signals and to assess the signals. We will discuss the first four elements with regard to generating signals and the last two in the next section about assessing signals. Where appropriate, we draw on our analysis of data from FDA's adverse event reporting database.⁴³ Unless otherwise stated, the data are from the period 1994-1999.

Key Information For An Adverse Event Reporting System	
Element	Description
Medical Information	Information such as laboratory tests, medical diagnosis, medical history, preexisting conditions, dose, frequency of use, and concurrent medications assist clinical staff in evaluating whether the product could have caused the adverse event.
Product Information	FDA needs to know the identities and concentrations of ingredients contained in the product to determine which ingredient may have caused the adverse event. It is also valuable for FDA to have some information about the product's safety, recommended dosing, claims, and the product's label.
Manufacturer Information	Information such as address and contact person help FDA contact manufacturers to obtain additional information. Often manufacturers have more clinical data and information that are not readily available to FDA. Also, manufacturers could provide FDA with product samples.
Contact Information on the Consumer	Information on the consumer of the dietary supplement is important in order to conduct follow up. A consumer can be identified through a variety of mechanisms that still maintain confidentiality.
Clinical Information	Information on the types of experiences in similar populations or in the past provide contextual information that could help FDA triage reports. This information can be obtained from large scale clinical trials, small research studies, and epidemiological studies.
Trend Analysis	A database with the capacity to conduct statistical analysis must be available and FDA needs to receive enough reports to conduct meaningful trend analyses.

Limited medical information. FDA could not obtain the medical records for 58 percent (464 of 801) of the reports it followed up on. To obtain medical records, FDA first must obtain the permission of the alleged injured party. However, FDA told us that it often has difficulty locating or reaching consumers. FDA may need to make repeated phone calls over weeks before contacting the consumer and securing access to medical information. And sometimes consumers refuse to release their medical records to FDA out of concern for their privacy. According to the General Accounting Office, FDA's credibility in attempting to restrict the sale and use of dietary supplements containing ephedrine alkaloids was undermined, in part, because FDA lacked sufficient medical records to establish a causal relationship between these supplements and the reported adverse events.⁴⁴

At least half of the reports in FDA's database came from consumers.⁴⁵ Consumers generally cannot provide as much medical detail or expertise as health professionals and therefore consumer reports tend to be less useful than those given by health professionals.⁴⁶ Because supplements are generally self-care products, it is not surprising that FDA receives the majority of supplement adverse event reports from consumers.

Twenty percent (527 of 2,547) of adverse events reports received by FDA came from health professionals. Physicians and pharmacists are often in the best position to provide critical medical information as well as to assist FDA in determining the relationship between the product and the event.

Limited product information. FDA was unable to determine the ingredients for 32 percent (1,153 of 3,574) of the products mentioned in adverse event reports. Dietary supplement manufacturers do not have to register their products with the FDA, in contrast to drug manufacturers. Therefore, FDA lacks a list of supplement products and their ingredients as a quick, easy reference when it receives a report. In addition, because dietary supplement manufacturers are not required to prove the safety of their products prior to marketing them, FDA generally has relatively little information about the safety of that particular product when it receives an adverse event report.

FDA lacks product labels for 77 percent (2,752 of 3,574) of the products associated with reports. In order to determine the ingredients of dietary supplements, FDA often depends on obtaining a copy of the product label. FDA officials told us that it is important that they obtain a photo of the actual label from the product consumed by the alleged injured party because dietary supplements sold under the same name often vary in the amount and type of ingredients they contain. For this reason, FDA cannot always assume that the ingredients in a product that it locates are the same ingredients contained in the identically named product consumed by the alleged injured party. In fact, we found a product with the same name and packaging in three different locations, yet each product listed different ingredients. Furthermore, dietary supplement manufacturers can claim "proprietary blends" and choose to exclude the actual quantities of particular ingredients on the labels of dietary supplements.⁴⁷

FDA lacks product samples for 69 percent (130 of 188) of the products for which samples were requested. Not only is it difficult for FDA to locate supplement consumers, but FDA also finds that supplement consumers often cannot or will not provide a product sample. Consumers may have discarded the remaining product, may want to hold on to it pending legal action, or may have sent it back to the manufacturer for a refund. Even when FDA has information about the ingredients contained in the consumed product, as stated on the label, a sample might need to be tested in order to determine the actual ingredients or the amount of each ingredient in the dose. Several recent studies highlighted the wide variation in the quality of supplement products.⁴⁸ One found that products contained varying amounts, ranging from 0 to 150 percent, of the labeled concentration of ingredients.⁴⁹

Another reason why FDA has difficulty determining the contents of dietary supplements is that it has not yet established good manufacturing practices for supplements, regulations on processes for ensuring ingredient quality and quantity. Although the Dietary Supplement Health and Education Act granted FDA the authority to establish good manufacturing practices for dietary supplements, it has not yet issued final regulations.⁵⁰ Without them, FDA lacks the explicit authority to examine manufacturer files that contain important information on how the product was made.

Limited manufacturer information. FDA receives few reports from manufacturers. Although we cannot confirm the number of reports FDA has received from manufacturers from FDA's database, FDA officials indicated that they have received fewer than 10 reports from manufacturers since 1993. Supplement manufacturers are not legally required to report adverse events. In contrast, prescription drug manufacturers are legally required to report adverse events as well as have a system in place to evaluate them.⁵¹ Thus, in 1999, FDA's Center for Drug Evaluation and Research, received 90 percent of its 280,000 adverse event reports for drugs and biologics from the manufacturers of those products. Pharmaceutical manufacturers must also do the investigative work that FDA sometimes does for dietary supplement reports.

FDA could not determine the identity of the manufacturer for 32 percent (1,153 of 3,574) of the products involved in the reports. FDA does not know the city and State where the manufacturer is located for 71 percent (644 of 904) of the manufacturers in its database. FDA does not routinely contact the supplement manufacturer when it receives an adverse event report on its product. One of the reasons FDA gives for not contacting manufacturers is that it cannot locate many of them. Manufacturers need to include only their name, city, and State on a product label if their phone number is listed in their local directory.⁵² If their phone numbers are not listed in the local directory, they must include their phone number on the label. However, FDA reports that dietary supplement companies have often moved from the addresses listed on the labels or exclude required information from their labels. In one instance, FDA received two reports of comas associated with a product, but when field inspectors tried to track down the manufacturer, they found a post office box belonging to an owner who had since moved and closed the

account. FDA was only able to locate the manufacturer after receiving more reports of adverse events and conducting further investigations.

Another difficulty in tracking manufacturers is that many supplements are sold through multi-level organizations.⁵³ In such a case, the consumer may know who the distributor is, but not the manufacturer. Distributors can be several layers removed from the manufacturer, making it increasingly difficult to track the source of the product. One inspector told us that he had resorted to searching State tax records to locate the manufacturer associated with a certain product.

On the other hand, some manufacturers have complained about not learning of adverse event reports involving their products until the media contacted them after obtaining the report from FDA's website. Unlike drug manufacturers, dietary supplement manufacturers are not required to register with FDA. Without such a database, FDA cannot easily contact the manufacturers and notify them that it received a report.

Limited contact information on the dietary supplement consumer. FDA could not follow-up with 27 percent (214 of 801) of the reports it tagged for follow-up. The primary reason is lack of enough contact information or some type of identifier of the alleged injured party to enable follow-up. Reporters may be reluctant to provide such information out of concern for privacy.

Limited ability to analyze trends. FDA has difficulty tracking and analyzing adverse event reports for three main reasons. First, FDA receives so few reports that it is difficult to conduct rigorous statistical analysis of them. As we have already pointed out, FDA received only 2,547 adverse event reports between 1994-1999.

Second, report quality is poor. As we have shown throughout the report, FDA is missing key information even after conducting follow-up. Missing information further weakens FDA's analysis.

Third, FDA has an inadequate computer database to track adverse event reports. The existing database emerged from FDA's need to log the reports that it receives. FDA did not design the database to analyze trends. For example, many of the data fields are empty in the majority of reports because the fields were created recently and the staff has not had the time to enter data retrospectively from its paper files. The database lacks automatic data edits that would remove common data entry errors such as misspellings or illogical entries, making it difficult to query for a specific word or entry. A number of the fields are defined poorly, complicating analysis. For example, all the ingredients for a product are listed in the same data field making it difficult to search for trends by a specific ingredient. It is also difficult to analyze across reports when a report involves more than one product.

FDA Lacks Vital Information to Adequately Assess Signals of Possible Public Health Concerns Generated by the Adverse Event Reporting System.

Limited clinical information. One key tool that FDA lacks in assessing signals is adequate clinical information. Information on the types of experiences in similar populations or in the past provide contextual information that could help FDA assess signals. This information can sometimes be obtained from large scale clinical trials, small research studies, and epidemiological studies. However, the current regulatory framework for dietary supplements does not require manufacturers to conduct these studies pre- or post-marketing. For this and other reasons, FDA has relatively little clinical information on particular products.

Some manufacturers and researchers have conducted such studies, but these studies by no means cover all dietary supplement products or ingredients. And the limited scientific literature on dietary supplements that does exist focuses almost exclusively on individual ingredients, such as certain botanicals or minerals. However, dietary supplements tend to contain multiple ingredients.⁵⁴

FDA does obtain some clinical information from its 75-day premarket notification requirements. But this applies only to dietary ingredients that were not marketed in the United States before October 15, 1994, and that have not been in the food supply as articles used as food without chemical alteration. To date, FDA has received 97 premarket notifications, covering 114 ingredients, 102 of which were new dietary ingredients (the remaining products/ingredients were found to be drugs or biologics).

FDA has some clinical information from the history of use. However, history of use information can be difficult to interpret as the information may be difficult to verify.

Limited information on consumer use. The size of the consumer population and the dosage taken by consumers helps FDA estimate the size of the potential threat to public health. Although millions of supplements are sold in hundreds of forms in thousands of locations, little evidence is available on how many doses of a particular product or ingredient are consumed. This dearth of information contrasts with the available information for prescription drugs for which the number of filled prescriptions is tracked and tabulated. Without consumer use information, it is difficult for FDA to know what the denominator is when evaluating the adverse event reports it receives and thus, the incidence of adverse events relating to a particular product or ingredient within the user population. This makes it difficult for FDA to determine the magnitude of safety concerns.

In appendix A we present a case study involving ephedrine alkaloids that illustrates the information FDA lacks to assess signals of possible public health concerns generated by the adverse event reporting system.

As a Result, FDA Rarely Takes Safety Actions Related to the Adverse Event Reporting System.

With limited information to draw upon to generate and assess signals, it is not surprising that FDA rarely reaches the point of knowing whether an action is needed in order to protect consumers. In our discussions with FDA officials and our review of available data, we sought to determine just how many safety actions FDA has taken that are attributable, at least in part, to the adverse event reporting system. We could not arrive at an exact number because of limitations in FDA's data systems, because of a lack of clarity over whether a safety action is, in fact, associated with adverse events, and even because of problems associated with defining the term "action." After a careful review, we did document 32 safety actions taken between January 1994 and June 2000 that FDA officials indicate were associated with adverse events. Depending on how one defines actions and with more information, there may well be more such actions in that time period. But, it is quite clear that at a time when more than 100 million people were taking dietary supplements, the number of FDA safety actions was strikingly low.⁵⁵ (See the table below and appendix B for additional information.)

FDA Safety Actions Related to the Adverse Event Reporting System (January 1994-June 2000)		
Action	Description	Number
Issue Consumer Warnings	FDA can alert the public in the form of press releases or discussion papers. FDA publishes these alerts on the Internet.	9
Disseminate "Dear Colleague" Letter to Health Professionals or Manufacturers	FDA can issue letters that provide advice and guidance on the use and marketing of dietary supplements to health professionals, manufacturers, and industry groups.	2
Require Additional Labeling	FDA can require supplement manufacturers to provide additional information on the product label, such as warnings, side effects, or dosage information.	1
Import Alert	FDA can prevent certain products or ingredients that are adulterated from entering the country.	1
Request Voluntary Product Recall	FDA can ask product manufacturers to recall a product voluntarily in lieu of mandating a recall.	15
Seizure of Products and Products that are Unapproved New Drugs	FDA can seize products that are illegal, such as products that FDA has concluded are unapproved new drugs rather than dietary supplements. FDA seizes particular lots of products or a particular manufacturer's products on a case-by-case basis.	4
Note: Due to limitations in FDA's data system, lack of clarity over whether or not a safety action is, in fact, associated with an adverse event, and problems in defining the term "action," there could be other actions that FDA has taken that are excluded from this table.		

It is important to recognize that just one action can have considerable impact on consumer safety. For example, FDA investigated a product upon receiving a report from a consumer complaining of nausea and irregular heart rates after she ingested a dietary supplement that was labeled as containing plantain. From its investigation, FDA determined that the product was contaminated with *Digitalis lanata*, a plant that contains heart stimulants, which under certain circumstances may lead to cardiac arrest. FDA widened its investigation and found other products labeled as containing plantain that were potentially contaminated with *Digitalis lanata*. This led FDA to issue a warning to consumers against certain products that were labeled as containing plantain. Simultaneously, FDA asked supplement manufacturers to recall these products.

On the other hand, we found several instances where FDA was unable to seize all the illegal products on the market (see box). Enforcing regulatory actions and ongoing monitoring are the responsibility of the FDA's Office of Regulatory Affairs, which coordinates enforcement and routine monitoring for all of FDA. Supplement cases must compete for enforcement resources with prescription drugs, medical devices, biologics, and food inspections, as well as outbreaks of food-borne illness. Ensuring compliance with actions taken against dietary supplements and routine monitoring of supplements are low priorities for FDA—generally prioritized below other FDA-regulated products, according to some FDA officials.

Lack of enforcement?

- D** In June, 2000, we purchased two self-described herbal Phen-Fen products in two national stores a few blocks away from our offices in Boston. FDA concluded that herbal Phen-Fen is an unapproved new drug in 1997.
- D** We found Internet sites selling the street drug alternative, "herbal ecstasy." These products were being marketed as safe alternatives to ecstasy, an illegal drug. One stated that its product "is an herbal formulation that is designed to specifically mimic the stimulating and prosensual effects of MDMA aka ecstasy." Another site simply stated "Herbal Ecstasy: an online store for items to get you *high*." FDA considers "any product that is promoted as a street drug alternative to be an unapproved new drug and a misbranded drug." We recognize that enforcing Internet sales may be difficult.

Public disclosure is ineffective. FDA's public disclosure of adverse events reports can also be considered a type of action. FDA's website is its main vehicle for providing information to consumers. The website contains access, with searching capabilities, to a public database on dietary supplement adverse event reports. However, this database has significant limitations: no evaluation of the listed adverse event reports, incorrect information among the reports, and the information is rarely updated. As a result, the website does a poor job of informing the public.

The public database's main limitation is that it fails to provide any FDA evaluation of the relatedness of the dietary supplement or a particular ingredient to the adverse event. The reports are posted as reported and exclude any FDA assessment. To illustrate this

shortcoming, we typed “lettuce,” an ingredient sometimes contained in herbal products, into the public adverse event database to determine whether any adverse events were associated with this clearly innocuous ingredient; the search found four adverse events, including two deaths. However the website made no mention of the fact that the event is unlikely associated with this ingredient.⁵⁶

Furthermore, some of the information in the database may be inaccurate because FDA was unable to contact the reporter to verify the information. In one case, a manufacturer was contacted by a consumer who had seen a report of an adverse event attributed to the manufacturer’s product on the FDA website. In fact, the manufacturer did not sell that product. When the manufacturer alerted FDA about the problem, FDA made the correction.⁵⁷

Finally, FDA rarely updates the database. As of October 2000, the most current information was from a October 20, 1998 report.

Although FDA’s website is its primary mode of disclosing public information, interested parties always have another option for obtaining information from government agencies through Freedom of Information Act requests. However, even this form of public disclosure is problematic for retrieving information on dietary supplement adverse event reports. FDA must maintain the confidentiality of personal medical information contained in the report file when processing such requests. That information provides essential information about a supplement’s role in a particular event. To avoid privacy violations, FDA removes any information that could identify an alleged injured party before releasing a file, a time-consuming and resource-intensive process. Industry representatives complain that, as a result of this redaction process, FDA takes a long time to fill these requests, thereby preventing the timely release of adverse event information.

RECOMMENDATIONS

Our evaluation of FDA's dietary supplement adverse event reporting system leads us to conclude that without further development of the overall regulatory framework for dietary supplements, the potential of the adverse event reporting system as a consumer safeguard is inherently limited.

FDA is aware of its limitations in terms of confirming signals generated from its system. In its dietary supplement strategic plan, it identified a number of measures that it expects to enact as soon as resources become available.^{58,59} Similarly, manufacturers acknowledging waning consumer confidence in the safety of products, have also called for changes.⁶⁰ And finally, the 1997 White House Commission on Dietary Supplement Labels and the General Accounting Office have both issued reports that address these concerns.⁶¹

In presenting our recommendations, we offer a blueprint for actions that can be taken over a reasonable period of time. We recognize that some of our recommendations may call for legislative or regulatory changes. We also recognize that FDA's resources are limited and that some of our recommendations may require additional resources.

RECOMMENDATION 1: Facilitate Greater Detection of Adverse Events.

FDA must make efforts to facilitate the reporting of adverse event reports to the system. Even with the best quality information, too few reports will minimize FDA's capacity to detect signals among adverse events reports (even the tightly controlled premarket clinical trials for pharmaceuticals, which usually contain around 3,000 subjects, fail to detect relatively rare adverse events during clinical trials). To increase the percentage of events reported, FDA should:

Require dietary supplement manufacturers to report serious adverse events to FDA for some products. Requiring supplement manufacturers to report serious adverse events would be valuable to FDA. However, such a requirement may not be necessary for all dietary supplements. FDA should determine the appropriate scope of this requirement. FDA already requires pharmaceutical manufacturers to report adverse events for all prescription and some over-the-counter drugs. FDA should recognize that if manufacturers are going to adhere to such a requirement, FDA first needs to convince them of the importance and adequacy of the system.

Contract with Poison Control Centers to obtain their adverse event reports on dietary supplements. In 1999, these Centers collectively received far more dietary supplement reports than FDA did in that same year. They clearly hold a wealth of reports that would be extremely useful. However, before contracting with these centers, FDA will have to grapple with two main complications. First, it will have to reconcile its

database technology with that of the Centers. Secondly, it will need to reconcile the two entities' conflicting privacy policies. The Centers consider product identity private information and, thus, have told FDA that they would remove any product codes from their reports unless FDA were to agree not to release product identities to the public.

Inform health professionals and consumers about the adverse event reporting system for dietary supplements. FDA should expand its outreach to health professionals by disseminating information about the supplement adverse event system, actions it has taken, and warnings about potentially harmful supplements. It should target not only physician and nurse organizations, but also professional organizations for pharmacists and practitioners of alternative and complementary medicine.⁶²

FDA may also want to consider requiring manufacturers to list their toll-free number on product labels especially if they are required to report adverse events to FDA. Another possibility is for FDA to require its toll-free number be placed on product labels.

RECOMMENDATION 2: Obtain More Information on Adverse Event Reports In Order to Generate Stronger Signals of Public Health Concerns.

Medical Information

Without the alleged injured party's medical records, FDA lacks crucial information for determining the likelihood that the adverse event was related to use of the dietary supplement. Too often, these records are missing from reports. To increase the probability of receiving medical records, FDA should:

Educate health professionals about the importance of including medical information in adverse event reports. When FDA conducts general outreach to health professionals about the dietary supplement adverse event reporting system, it should present information on the role that medical records play in assessing adverse events. FDA should conduct further outreach to encourage health professionals to obtain consent from their patients to release their medical records to FDA.

Product Information

One of the main reasons FDA has difficulty determining which, if any, supplement ingredient or combination of ingredients is most likely to have caused the adverse event is that it is often unable to determine the precise ingredients contained in the supplement that was consumed. To improve the quality and quantity of this product information, FDA should:

Require dietary supplement manufacturers to register their products with FDA. FDA often has difficulty obtaining the product identified in the report. A complete product registry would allow FDA to instantly access a list of all of the ingredients in a

particular product and determine the product manufacturer's name as soon as an adverse event report was received.

Notify manufacturers when FDA receives a serious adverse event report. Alerting manufacturers to adverse events in which their products have been mentioned would give FDA the opportunity to obtain more product information from the manufacturer and could also improve FDA-industry relations. FDA could use this interaction with the manufacturer to obtain a copy of the product label, information on the product's ingredients, or information about any past adverse events that the manufacturer was aware of associated with that product. If FDA notified manufacturers as soon as the adverse event was reported, manufacturers may be more helpful in sharing information about their products with FDA in a timely manner. Manufacturers could also assess the product's safety profile in a more timely fashion. Clearly, it would be much easier for FDA to notify manufacturers if it had access to a complete registry of dietary supplement manufacturers.

Manufacturer Information

Require dietary supplement manufacturers to register with FDA. A registry of manufacturers would enable FDA to quickly and easily contact a manufacturer whose product was associated with an adverse event. It would also allow FDA to disseminate warnings, recalls, or other pertinent information to the manufacturers that might be affected by a particular action. Registering with FDA could be a simple process—a web-based form, for example—and would prevent FDA from wasting scarce resources while furthering its mission of protecting consumers.

Contact Information on the Consumer

FDA is often stymied in its efforts to contact the alleged injured party to gather more information about the product used, the circumstances under which it was used, and any preexisting conditions that the supplement consumer may have had. It is essential that FDA confirm this information with the consumer of the supplement because, otherwise, the validity of the adverse event report may be called into question. To ensure obtaining this contact information, FDA should:

Emphasize to health professionals and consumers the importance of providing a way to identify the alleged injured party in reports. Reporters to the adverse event reporting system must be aware that, without some type of identifier of the alleged injured party, FDA may be unable to take further action to investigate the report. We recognize that confidentiality is a concern. FDA must ensure that the reporter and the alleged injured party will be unidentifiable under any circumstances, including under a Freedom of Information Act request. Once it is confident that it can ensure the confidentiality of this information, it should make this fact known to reporters of adverse events.

Trend Information

Develop a new computer database to track and analyze adverse event reports. The quality of each piece of information in the adverse event reporting system must be improved before FDA can effectively detect trends. Beyond that, to improve its ability to generate signals from the system, FDA should reengineer its database. The current database was designed for administrative purposes, not for analyzing trends. FDA needs a new system that will allow it to rigorously analyze adverse event reports on an ongoing basis. The system should allow for querying by ingredients as well as products and types of adverse event reaction. It should also have automatic data edits so that queries will not be undermined due to misspelled or miskeyed entries. FDA should work in partnership with the industry to redesign the system, as the industry has complained extensively about the current system's operations. FDA has already called for this in its strategic plan.

RECOMMENDATION 3: Obtain Vital Information to Adequately Assess Signals Generated by the Adverse Event Reporting System.

The central weakness we found is FDA's inability to adequately confirm signals that are generated from the system.

Perhaps the largest problem that FDA faces is the paucity of scientifically robust research on dietary supplements that is available in the event that a particular supplement product or ingredient generates a signal of possible public health concern. Below are some ways that FDA could increase the quality and quantity of clinical data available to them:

Issue guidance on the type of safety information that manufacturers should include in the 75-day premarket notification requirement for new dietary supplement ingredients. Because the 75-day requirement, though limited, represents the only premarket information that FDA is authorized to obtain on dietary supplements, it should take full advantage of its authority. Yet no guidelines currently exist, undermining the usefulness of such a requirement. We encourage FDA to collaborate with industry in developing these guidelines, another item on FDA's strategic plan.

Explore the possibility of a monograph system for dietary supplements. Monographs are point papers on particular products or ingredients that contain safety and efficacy information. FDA has contracted with The National Academy of Sciences to describe a process for developing a monograph system for dietary supplements.⁶³ Such a system would allow FDA to gather, in a systematic fashion, safety information that it could base safety decisions upon. In addition, FDA could require manufacturers to adhere to the monographs in the future.

Collaborate with the National Institutes of Health in setting a research agenda addressing safety issues. Another way that FDA can gain clinical information on supplements is by collaborating with the National Institutes of Health's Center for

Alternative Medicine and Office of Dietary Supplements. FDA and NIH already work with another through a trans-agency committee dedicated to supplements. They should continue to work together and should begin to address specific safety issues that arise from the system.

Assist industry and the United States Pharmacopeia in standardizing dietary supplement ingredients, particularly botanicals. Standardized ingredients would allow FDA to recognize trends in adverse events associated with products containing common ingredients. Ingredient names should also be standardized so that a particular ingredient cannot be listed under multiple names, adding to FDA's difficulty in conducting trend analysis. FDA and industry have been working with the United States Pharmacopeia, a not-for-profit standard-setting body, to develop such quality standards. Although it has been setting standards for vitamins and minerals for 10 years, its efforts in setting standards for botanical dietary supplements have been delayed due to the complexity of their ingredients.⁶⁴ Nevertheless, it is currently considering a voluntary demonstration program for assuring the quality of botanical supplements in the marketplace through conformity testing of ingredient and product standards as well as performance standards for manufacturing.⁶⁵ Such a program, though valuable, would be limited in its ability to protect consumers because it would be voluntary; it would not address botanicals' health claims or safety issues, and United States Pharmacopeia would not enforce adherence to these standards. Despite these limitations, we encourage FDA to continue working with this body on this effort. Ultimately, FDA should work towards making adherence to quality standards mandatory for supplement manufacturers.

Expedite the development and enactment of good manufacturing practices for dietary supplement manufacturers. Standardized ingredients must be complemented by FDA enforcing those standards through good manufacturing practices. These are essential for FDA to be assured of the precise contents of each batch of supplements that is manufactured. Such information is crucial when an adverse event occurs following the use of a particular product because it allows FDA to verify the amount of each ingredient contained in the product and the possibility of contamination by another substance. Without them, FDA is hard-pressed to investigate supplement manufacturers because it has few standards to which to hold them accountable. FDA's development of good manufacturing practices, which is in FDA's strategic plan for dietary supplements, is nearing completion and will be integrated, when possible, into United States Pharmacopeia's aforementioned standardization efforts.⁶⁶ As so much of FDA's capacity to oversee supplements rests on enforceable good manufacturing practices, we urge FDA to expedite developing and enacting of them.

RECOMMENDATION 4: Disclose More Useful Information to the Public about Dietary Supplement Adverse Events.

FDA needs to provide data to the public so that the consumer can, to some extent, evaluate the likelihood that the adverse event was related to consuming the supplement. One way in which FDA can accomplish this is by placing summary data on its website. For example, FDA could indicate the number of adverse events it has received with a particular product or ingredient. FDA could also update the adverse event reporting information on its website more regularly. Public disclosure loses its force as a consumer protection mechanism when the information is out-of-date. Over time FDA may want to explore the possibility of indicating the likelihood that such events may or may not be associated with the product or ingredient.

COMMENTS ON THE DRAFT REPORT

We received comments on our draft report from the Food and Drug Administration (FDA). We solicited and received comments from three trade associations: the Consumer Healthcare Products Association, the American Herbal Products Association, and the Council for Responsible Nutrition. We also solicited and received comments from two public interest organizations: Public Citizen's Health Research Group and the Center for Science in the Public Interest.

On the basis of these comments we made several changes that are reflected in this final report. Some involved minor technical changes, and others involved brief elaborations to clarify and add context. In two instances we modified our recommendations to target them more effectively and to minimize regulatory burden. We limited the scope of mandatory reporting of adverse event reports to events that are both serious in nature and fall under a certain subset of products to be determined by FDA. Similarly, instead of calling for FDA to notify manufacturers of all adverse event reports it receives, we called for FDA to notify manufacturers of serious reports only.

Below we summarize some of the larger issues raised in the comments and provide our response. (See appendix C for the comments in their entirety.)

Food and Drug Administration

FDA thought that our findings were a fair assessment of the challenges it faces in using the adverse event reporting system. FDA also agreed with the majority of our recommendations. As part of its comments, it categorized our recommendations into three areas: (1) tasks that it can currently accomplish, (2) tasks that require additional resources, and (3) tasks that require legislative changes as well as additional resources. FDA pointed out that for many of those recommendations that fall into the first two categories, it already is taking steps to implement them. FDA has included among its top priorities publishing good manufacturing practices and establishing a system for making adverse event reports available to manufacturers in a timely fashion. In addition, FDA is working with the National Institutes of Health to highlight research areas and with the Institute of Medicine to categorize dietary ingredients based on safety concerns.

FDA has not taken any steps to implement our recommendations that fall into the third category, requiring both legislative authority and additional resources. This includes requiring manufacturers to report adverse events associated with dietary supplements and requiring manufacturers and their products to be registered with FDA. In its comments, FDA took no position on these recommendations.

FDA is making progress toward improving the system that is in line with the recommendations we call for in this report. Many of our recommendations are already included among FDA's top priorities. We encourage FDA to seek the authority it needs to require manufacturer and product registration and mandatory manufacturer reporting of adverse events.

Trade Associations

The three trade associations provide some support for a number of our recommendations, but, for the most part, they were highly critical of both our findings and recommendations. While we disagree with the thrust of their comments, we believe that they help sharpen the issues that need to be addressed as part of any reform.

One of their major critiques was that we chose not to evaluate the internal operating procedures of FDA's adverse event reporting system. This decision, the trade groups suggest, precluded us from making more practical recommendations on how the system could be improved. As one respondent also noted, with little support for broader recommendations on how the system could be enhanced. We recognize that there could be value to a procedural study. FDA should be doing everything it can to make sure the current system operates as effectively as it possibly can. But we strongly disagree with the comment that the current system could work adequately by simply improving internal operating procedures. The adverse event reporting system, as we document extensively, cannot provide an adequate consumer safeguard without further development of the overall regulatory framework for dietary supplements.

Another significant critique from the trade groups was that we failed to view dietary supplements in the context of a food-related system. This failure, they claim, led us to call for more extensive regulatory interventions, similar to those for prescription drugs. In response, our inquiry made us acutely aware of how little information FDA has available to identify whether adverse events about dietary supplements provide signals of possible public health concerns and to assess those signals. Without an improved capacity to obtain such information, FDA's adverse event reporting system will continue to fall short of its potential.

Still another critique is that our report reflects a negative view of dietary supplements and fails to recognize their role as self-care products that so many consumers value. We regret any implication of such a negative view. We have sought to focus strictly on how well the current system works and how it could work better. If the kind of recommendations we call for are enacted, we suggest that consumers would have more extensive and useful information available to them on these self-care products. Consumers also could have more confidence that an adverse event reporting system was providing them with a valuable measure of protection.

Public Interest Organizations

The two public interest organizations strongly supported our report. Both expressed support for all of our recommendations. Their main critique was that we did not go far enough. One group called for legislative changes that, over time, would significantly enhance FDA authorities. The other called for FDA to support a systematic study of dietary supplement safety and efficacy.

While our evidence did not allow us to go as far as these organizations would like, it did lead us to emphasize that a comprehensive set of changes must be carried out if the adverse event reporting system is to provide an adequate consumer safety valve.

FDA's Experiences in Overseeing Ephedrine Alkaloids

The purpose of this case study is not to judge the safety of botanical forms of ephedrine alkaloids. Rather, we intend to use the example of dietary supplements that contain ephedrine alkaloids to illustrate that, even when FDA receives a strong warning signal from its adverse event reporting system, severe limitations inhibit FDA's ability to confirm the signal. Therefore, FDA's ability to take action is undermined. FDA's attempted regulation of ephedrine alkaloids is, by no means, representative of other actions attempted by the agency. We choose to highlight it because it exemplifies many of the shortcomings in the current adverse event reporting system for dietary supplements.

After a brief background on the subject, we describe the key elements in FDA's oversight of ephedrine alkaloids and we discuss criticisms directed at FDA. Finally, we provide our own commentary on the criticisms.

Background

Ephedrine alkaloids may be derived from plants (botanicals) or synthesized chemically. The botanical form is generally derived from *Ephedra sinica*, also known as ma huang, but it may come from other botanical sources. The most common uses for supplements containing botanical ephedrine alkaloids are for losing weight and boosting energy.⁶⁷ Botanical forms of ephedrine have been used in traditional Chinese medicine for thousands of years to treat asthma, colds, coughs, fever, and nasal congestion. FDA currently regulates synthetic forms of ephedrine as over-the-counter drugs to treat asthmatic symptoms. Synthetic ephedrine (ephedrine HCl) is "generally recognized as safe and effective" for those 12 and older when used as a bronchodilator at doses up to 25 mg per dose not to exceed 150 mg a day.

According to FDA, between 1993, when it began a new system to collect dietary supplement adverse event reports, and March, 2000, it received 1,173 adverse event reports associated with the use of products that contain, or were suspected to contain, ephedrine alkaloids. Many of these reports involved serious events, including some deaths. They also tended to involve young people; about 60 percent of the alleged injured parties were under the age of 40.⁶⁸ The reports that FDA received containing ephedrine alkaloids comprised about half of the total reports that FDA received relating to *all* dietary supplements. The size and severity of reports associated with botanical ephedrine alkaloids raised concerns within FDA about the safety of this ingredient and prompted FDA to learn more about potential health concerns relating to ephedrine alkaloids. As of September, 2000, FDA had not taken any action to regulate ephedrine alkaloids, although during this time period many States and industry groups have taken safety measures related to these supplements.^{69,70}

Below we present the major events in FDA's attempt to ensure the safety of dietary supplements containing ephedrine alkaloids:

July, 1993: FDA issued its first public warning of possible safety problems associated with dietary supplements containing ephedrine alkaloids. The received reports described events such as hypertension, palpitation, neuropathy, myopathy, psychosis, stroke, and memory loss.⁷¹

February, 1995: FDA issued a press release warning consumers against a particular dietary supplement, "Formula One," which contained both ephedrine alkaloids and a botanical containing caffeine.⁷²

October, 1995: FDA convened a working group of its Food Advisory Committee that comprised medical and other scientific experts outside of FDA as well as consumer and industry representatives, to consider public health concerns associated with the use of dietary supplements containing ephedrine alkaloids. The group agreed that these supplements may cause consumers to experience serious adverse events, but could not agree on a specific dosage limit or warning statement.⁷³

April, 1996: FDA warned consumers not to purchase or consume ephedrine-containing dietary supplements with labels that portray the products as alternatives to illegal street drugs, because they pose significant health risks.⁷⁴

August, 1996: FDA convened its full Food Advisory Committee to address safety concerns about ephedrine alkaloid-containing dietary supplements. Half of the committee believed that no safe levels of ephedrine alkaloids in dietary supplements existed. The Committee did not reach a consensus on safety recommendations.⁷⁵

June, 1997: FDA published a proposed rule on dietary supplements containing ephedrine alkaloids.⁷⁶ The rule contained the following provisions:

- e Must contain less than 8 mg of ephedrine alkaloid per serving, and the recommended use must not exceed 24 mg within 24 hours;
- e Must carry a label stating that the product should not be used for more than 7 days;
- e May not be combined with other known stimulants, such as caffeine;
- e May not have a labeling claim that requires long-term intake to achieve purported effect;
- e Must contain a statement in conjunction with claims that encourage short-term, excessive intake that ingesting "more than the recommended serving may result in heart attack, stroke, seizure, or death"; and
- e Must contain a specific warning on the product label.

November, 1997: FDA warned consumers against dietary supplements, most of which contain ephedrine alkaloids, being promoted as natural herbal alternatives to the prescription drug combination “fen-phen” (fenfluramine and phentermine).⁷⁷

July, 1999: The General Accounting Office (GAO) released the report, “Dietary Supplements: Uncertainties in Analyses Underlying FDA’s Proposed Rule on Ephedrine Alkaloids.”⁷⁸ Congress requested a report following challenges to FDA’s Proposed Rule by the supplement industry and the Small Business Association. GAO’s report criticized the quality of information upon which the FDA’s Proposed Rule was based. Specifically, it found that FDA relied almost exclusively on poorly documented adverse event reports to write its Proposed Rule. GAO pointed out that the majority of the adverse event reports were incomplete; that FDA did not demonstrate the causality between ephedrine alkaloids and the adverse event reports; and that the Rule’s recommended dosages and duration of use were based solely on poorly documented adverse event reports. However, GAO stated that “FDA was justified in determining that the number of adverse event reports relating to dietary supplements containing ephedrine alkaloids warranted their attention and consideration of steps to address safety concerns.”⁷⁹

April, 2000: FDA formally withdrew many of the provisions from its Proposed Rule about ephedrine alkaloids, pending further data collection and analysis.⁸⁰ FDA withdrew the following provisions:

- e Dosage limits and limits to maximum daily intake;
- e Method of ensuring manufacturer compliance with above provision;
- e Limits on duration of supplement use; and
- e Prohibition of claims about the supplement, such as those that would encourage use that exceeds the proposed limits of individual dosages, daily intake, and duration of use.

August, 2000: The Department of Health and Human Service’s Office of Women’s Health convened a public meeting to discuss the ongoing safety assessment of dietary supplements containing ephedrine alkaloids. The meeting was not intended to deliberate on possible regulatory actions. FDA stated that these deliberations would not take place until it believes that the “available scientific information has been fully discussed.”⁸¹ The meeting set out to answer four main questions:

- e What positive and adverse physiological actions would be expected of botanical ephedrine alkaloids based on their known constituents? Does the available information show an association between the use of dietary supplements and adverse events?
- e Are there any circumstances for which there are well established indications for the use of dietary supplements containing ephedrine alkaloids? What doses and durations are needed to address those indications?

- e How would one characterize the seriousness or severity of the risks of ephedrine alkaloids labeled for weight loss and exercise enhancement taking into account issues such as user demographics, the amount consumed by the population, use with other stimulants, or the added stress of exercise or individual sensitivities?
- e Are the outcomes associated with these products affected by dosage, by user characteristics or behaviors (such as combining use with other stimulants or compounds)? Are outcomes affected by duration of exposure?⁸²

Some Criticisms of FDA's Proposed Rule of Dietary Supplements Containing Ephedrine Alkaloids

The following represent some of the criticisms directed towards FDA in response to its Proposed Rule on dietary supplements containing ephedrine alkaloids. Many of the criticisms were voiced by industry representatives during Congressional hearings about the Rule. Others appear in the 1999 GAO report. They are not direct quotes and may be attributed to many individuals and groups. We also provide our own commentary on how the criticism demonstrates shortcomings in the adverse event system as well as other regulatory mechanisms that have a direct impact on the adverse event reporting system.

Criticism: *FDA's proposed serving size (8 mg) is based, in large part, on its analysis of a negligible number of product samples associated with adverse event reports.*

Commentary: Dietary supplement manufacturers are not required to register the formulations of their products with FDA. In addition, FDA has not yet established Good Manufacturing Practices for dietary supplements that may provide the agency with more confidence in assuming that products contain what is listed on their labels, and in the quantities listed. Thus, FDA depends overwhelmingly on consumers to provide samples of the consumed products associated with reports. We already pointed out that FDA has difficulty obtaining these samples.

Criticism: *FDA's case for the safety actions on supplements containing ephedrine alkaloid relies almost entirely on its analysis of adverse event reports, rather than on controlled research.*

Commentary: Under the Dietary Supplement Health and Education Act, supplement manufacturers may market certain ingredients without any premarket review by FDA. The Act does not require that manufacturers prove the safety of ingredients in a controlled clinical setting; the burden is on FDA to prove that the ingredient is adulterated. Because manufacturers do not have to conduct preapproval studies to determine appropriate dosages, side effects, and incidence of adverse events, FDA does not have this information available when it has concerns about the safety of an ingredient or product. Controlled clinical trials take years to conduct, a time frame that may seem

both excessive and untenable when an ingredient seems to pose serious health problems.⁸³

Criticism: *Many of the adverse event reports that FDA relies upon for its safety assessment of supplements containing ephedrine alkaloids lack adequate information on how the product was used.*

Commentary: The GAO found that, of a sample of reports, 39 percent lacked information on the amount of product consumed, 41 percent lacked information on the frequency with which the product was consumed, and 28 percent lacked information on the duration for which the product was consumed.⁸⁴ Such incomplete data undermine FDA's ability to properly analyze the adverse event reports that it does receive, precluding it from being able to conclusively determine a safe dosage, frequency, and duration. For other FDA-regulated products, data on dosage, frequency, and duration of use are established by the manufacturer in controlled clinical settings prior to market as part of FDA's preapproval process.

Criticism: *FDA lacks denominator data and, thus, data on the incidence of adverse events associated with supplements containing ephedrine alkaloid.*

Commentary: Because the law does not require any registration of either dietary supplement manufacturers or products, FDA has no way of quickly gauging the number of products sold. Also, because there may be hundreds of products containing a particular ingredient, any effort on FDA's part to estimate the consumed doses of a particular ingredient is riddled with difficulties. In situations where FDA feels a sense of urgency to act, an attempt to obtain reasonably accurate denominator data is too burdensome and time consuming.

Criticism: *Adverse event reports are unreliable because they predominantly come from consumers.*

Commentary: Dietary supplements are self-care products. Health care professionals often are not aware that their patients are taking dietary supplements. Supplement manufacturers are not required to report adverse events associated with their products to FDA, as they must for prescription drugs, and they virtually never do. Thus, FDA is largely dependent upon consumer reports to alert them of possible concerns with dietary supplements.

FDA Actions Spurred by the Adverse Event Reporting System January 1994 - June 2000

Below is a list of FDA safety actions based on the AER system that we were able to document. Due to limitations in FDA's data systems, lack of clarity over whether or not a safety action is in fact associated with an adverse event, and problems defining the term "action," there could be other actions that FDA has taken that are not included below.

Consumer Warnings

"Formula One": In February 1995, FDA warned consumers not to purchase or consume the "Formula One" products. These product were marketed for weight loss. The products may cause irregular heart beats and heart attacks. (See appendix A).

Ephedrine: In April 1996, FDA warned consumers not to purchase or consume supplements containing ephedrine that are portrayed as alternatives to street drugs. Ephedrine is a stimulant that may cause seizures, heart attacks, and strokes.

Gamma hydroxybutyric acid (GHB): In February 1997, FDA reissued its 1990 warning that GHB is an unapproved new drug and as such cannot be marketed as a dietary supplement. GHB typically is marketed as an alternative to steroids. Problems associated with its use include vomiting, dizziness, seizures, and even death.

"Chomper": In May 1997, FDA warned consumers not to purchase or consume the product "Chomper" marketed as an herbal laxative. FDA determined that this product was contaminated with the plant *Digitalis lanata*, which can cause rapid heart rate and even heart attacks.

"Plantain": In June 1997, FDA warned consumers not to purchase or consume certain products labeled as containing plantain, sometimes marketed as herbal laxatives. FDA found that some of these products were contaminated with the plant *Digitalis lanata*, which can cause rapid heart rate and even heart attacks.

5-hydroxy-L-Tryptophan (5-HTP): In August 1998, FDA found impurities in (5-HTP) products which are marketed as sleep aids and mood enhancers. One of the impurities, termed "Peak X" is similar to an impurity that was found in products containing L-tryptophan in 1989. The use of L-tryptophan products was associated with eosinophilia-myalgia syndrome. This syndrome is characterized by elevations in a particular type of white blood cell and severe muscle pain. FDA encouraged consumers to report any adverse events associated with these products.

Gamma Butyrolactone (GBL): In January 1999, FDA alerted consumers not to purchase or buy products containing GBL. These products tend to be marketed as muscle builders, stress relievers, and sleep aids. When ingested, GBL is transformed in the body to gamma hydroxybutyrate (GHB), an unapproved new drug, which can lead to unconsciousness and sometimes death.

Gamma Butyrolactone (GBL) related products: In May 1999, FDA warned consumers not to purchase or ingest products labeled as containing 1,4 butanediol (BD), tetramethylene glycol, gamma butyrolactone, or 2(3H)-furanone di-hydro. Products containing these ingredients are usually marketed as sleep aids. These products may cause low respiratory rates, unconsciousness, seizures, and possibly death.

“Triax Metabolic Accelerator”: In November 1999, FDA warned consumers not to purchase or consume the product Triax Metabolic Accelerator, marketed as a weight loss product, because FDA determined it was an unapproved new drug that contained a potent thyroid hormone. The hormone may cause heart attacks and strokes.

Dear Colleague Letters

Aristolochic Acid: In May 2000, FDA issued a letter to the industry and health care professionals warning that several botanical products were found to contain aristolochic acid, which can cause nephropathy and end-stage renal disease.

Gamma Butyrolactone (GBL): In June 1999, FDA issued a letter to health care organizations asking them to disseminate information warning consumers not to purchase or consume GBL-related products. (See prior listing.)

Require Additional Labeling

Iron: In January 1997, FDA required the following warning on dietary supplements containing iron or iron salts. “WARNING: Accidental overdose of iron-containing products is a leading cause of fatal poisoning in children under 6. Keep this product out of reach of children. In case of accidental overdose, call a doctor or poison control center immediately.” 21 C.F.R. 101.17.

Voluntary Recalls

“Plantain”: In October 1997, FDA asked 12 manufacturers to recall plantain products suspected to be contaminated with *Digitalis lanata*. In April 1998, FDA asked another manufacturer to recall its product contaminated with *Digitalis lanata*. (See prior listing.)

Gamma Butyrolactone (GBL): In March 1999, FDA asked a manufacturer to recall its product containing GBL. In December 1999, FDA asked another manufacturer to also recall its product containing GBL.

Import Alerts

Aristolochic Acid: In May 2000, issued an import alert preventing botanical ingredients that contain aristolochic acid from entering the country. (See prior listing.)

Product Seizures and Products That are Unapproved New Drugs

“Herbal Phen-Fen”: In November 1997, FDA concluded that products promoted as “natural” or “safe” alternatives to the weight-loss drugs phentermine and fenfluramine are, because of their intended use, unapproved new drugs. These products do not contain prescription drugs. Instead, many contain ephedra, a stimulant that may cause strokes and heart attacks. (See prior listing.)

Gamma Butyrolactone (GBL): In 1999, FDA concluded that GBL is an unapproved new drug because it is transformed in the body to gamma hydroxybutyrate (GHB). FDA initiated a seizure action in April 1999 against these products. FDA also brought criminal cases against people distributing GBL and GHB.

“Triax Metabolic Accelerator”: In November 1999, FDA concluded that it was an unapproved new drug. (See prior listing.) FDA initiated a seizure action against Triax in December 1999.

“Street Drug Alternatives”: In March 2000, FDA determined that any products marketed as an alternative to street drugs are not dietary supplements because they intend to alter mental states, not supplement the diet. FDA considers these products unapproved new drugs and, as such, they cannot be marketed as a dietary supplement.

Comments on the Draft Report

In this appendix, we present the full comments of all parties that responded to our draft report. In order, the comments are from the following parties:

- e Food and Drug Administration
- e Consumer Healthcare Products Association
- e American Herbal Products Association
- e Council for Responsible Nutrition
- e Public Citizen's Health Research Group
- e Center for Science in the Public Interest

**DEPARTMENT OF HEALTH & HUMAN SERVICES****Food and Drug Administration****Memorandum**

Date: APR - 6 2001

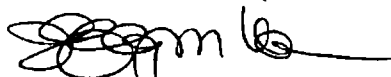
From: Acting Senior Associate Commissioner for
Management and Systems, FDA

Subject: Agency's Comments, OIG Draft Report: "Adverse Event Reporting for
Dietary Supplements", OEI-01-00-00180

To: Acting Inspector General
Michael F. Mangano

Thank you for the opportunity to review and comment on the Office of Inspector General's draft report, "Adverse Event Reporting for Dietary Supplements", OEI-01-00-00180. The Agency prepared General and Technical Comments for your consideration.

If you need additional information, please contact Loretta W. Davis, (301) 827-4809.



Jeffrey M. Weber

Attachments

cc: Elise Stein

FDA's Comments on the Office of Inspector General's (OIG's) Draft Report Regarding
FDA's Adverse Event Reporting System for Dietary Supplements

Thank you for the opportunity to review the OIG's draft report regarding our Adverse Event Reporting System for Dietary Supplements. FDA believes the draft is a fair assessment of the challenges FDA faces in the regulation of dietary supplements without a fully operational adverse event reporting system. As the report accurately states, in order to implement many of the OIG's recommendations, additional resources and/or legislative changes will be necessary.

FDA would like to offer the following general comments:

1. The dietary supplement industry has grown exponentially since the enactment of the Dietary Supplement Health and Education Act of 1994 (DSHEA). Surveys show that over 158 million consumers use dietary supplements.¹ As the overall use of these products increases, so does the potential for adverse effects. FDA's Adverse Event Reporting System for dietary supplements provides an essential tool for identifying potential safety problems that may be associated with the use of a particular product or type of products already in the marketplace that need to be investigated and critically evaluated.
2. In January 2000, FDA published its overall Dietary Supplement Strategic Plan. This plan incorporates substantial stakeholder input and provides a road map to fully implement DSHEA. It is a science-based regulatory program, that will provide consumers with a high level of confidence in the safety, composition, and labeling of dietary supplements. The "Safety" category of the Dietary Supplement Strategic Plan includes a section on adverse event reporting. This section is broken down into four activities: System Enhancement, Timely Release of Reports, Clinical Evaluation and Follow-Up, and Outreach.
3. Later this spring, FDA will submit to Congress, as requested, a report on the cost to fully implement the Dietary Supplement Strategic Plan. Additional funds for FDA's adverse event reporting system for dietary supplements were included in the President's budget for Fiscal Years 2000 and 2001, but no additional funds were provided. The Agency is hopeful that this report to Congress will better demonstrate the funds needed to fully implement FDA's dietary supplement activities.
4. Absent additional funding, FDA is proceeding incrementally, within available resources, on a year-to-year basis. FDA's accomplishments in FY200 were published in the CFSAN "Report Card" in December, 2000. These accomplishments included eliminating the prior FOI backlog for dietary supplement adverse events. In January 2001, CFSAN published its FY2001 program priorities. These priorities are broken down into A and B List items, with A items being given top priority and B items being completed when Agency resources allow. CFSAN has included the following activities as "A" list items for FY2001:

¹ PREVENTION Magazine's Survey of Consumer Use of Dietary Supplement, 200, p. 4.

- Publish dietary supplement good manufacturing practices (GMP) proposed rule and conduct outreach program;
- Establish a system for making adverse event reports (AERs) promptly available to manufacturers that includes timely redaction of confidential information;
- Work with the National Academy of Sciences' (NAS) Institute of Medicine (IOM) to review dietary supplement safety;
- Develop mechanisms to expedite dietary supplement adverse event investigations and enhance timely clinical assessment of dietary supplement AERs;
- Complete and disseminate a dietary supplement research plan;
- Submit a report to Congress summarizing the total funding spent in FY2000 to assess the safety of dietary supplements, including related costs required to meet the statutory burden of proving adulteration under DSHEA; and
- Submit a report to Congress on the cost to implement the Dietary Supplement Strategic Plan.

CFSAN has included the following activities as "B" list items for FY2001:

- Develop an approach for ensuring inclusion of appropriate safety information within 75-day notifications;
- Enhance and improve the dietary supplement website and create a "list serve" for dietary supplement topics;
- Prepare a regulatory guidebook for industry;
- In conjunction with NAS/IOM, investigate criteria and options for evaluating emerging science relative to dietary supplements.

5. FDA has already begun addressing a number of recommendations from the OIG report. For example:
 - FDA has made some progress in designing a new, single comprehensive computer system for CFSAN to track and analyze adverse event reports, with particular emphasis on dietary supplements;
 - FDA is working with the Office of Dietary Supplements and the National Center for Complementary and Alternative Medicine at the National Institutes of Health;
 - FDA has entered into a contract with the Institute of Medicine/National Academy of Sciences entitled "Framework for Evaluating the Role of Dietary Supplements in Health." The contract requires, among other things, that the committee develop a proposed framework for categorizing and prioritizing dietary supplement ingredients based on safety issues;
 - FDA has drafted proposed Good Manufacturing Practices (GMP) regulations and they are currently being reviewed by the new Administration; and
 - CFSAN has an established Website, with a recently updated link to dietary supplements.
6. FDA agrees with the general direction of the OIG's recommendations, although the Agency can take no official position on those recommendations needing legislative change at this time. The following chart categorizes into three groups, as follows: (a)

those recommendations that could likely be accomplished under current law with current resources; (b) those that, would require additional resources under current law; and (c) those that would likely require legislative changes and additional resources.

OIG's Recommendations -- Draft Report

<u>Recommendations</u>	Could Accomplish with Current Law and Current Resources	Could Accomplish under Current Law but Would Require More Resources	Would likely Require Legislative Changes and Additional Resources
Require dietary supplement manufacturers to report adverse events to FDA		X ²	
Contract with Poison Control Centers to obtain their adverse event reports on dietary supplements		X	
Inform health professionals and consumers about the adverse event reporting system for dietary supplements	X, to start	X, for enhanced system	X (to list FDA's telephone # on all dietary supplement labels) ³
Educate health professionals about the importance of including medical information in adverse event reports	X, to start	X, for enhanced system	
Require dietary supplement manufacturers to register their products with FDA			X
Require dietary supplement manufacturers to register with FDA			X
Notify manufacturers when FDA receives an adverse event report	X, to start	X, enhanced system ⁴	

² DSHEA is silent on this point; FDA is evaluating whether or not such reporting could be required under current law.

³ Some states already require these types of labels on the products.

⁴ Subject to restrictions under Privacy Act.

OIG's Recommendations – Draft Report

Recommendations	Could Accomplish with Current Law and Resources	Could Accomplish under Current Law but Would Require More Resources	Would Likely Require Legislative changes and Additional Resources
Emphasize to health professionals and consumers the importance of providing a way to identify the alleged injured party		X (FOIA, Privacy issues) ⁵	
Develop a new computer database to track and analyze adverse events		X, initial efforts underway, additional resources needed for completion	
Issue guidance on the type of safety information that manufacturers should include in the 75-day notification requirement for new dietary supplement ingredients	X, to start ("B" List for FY2001)	X, additional resources needed for extramural contract	
Explore the possibility of a monograph system for dietary supplements that would contain safety information on particular ingredients, particularly botanicals	X, to start (2 year process started last year)	X, to do comprehensively	
Collaborate with the National Institutes of Health in setting a research agenda addressing safety issues	X, already underway		
Assist industry and the United States Pharmacopeia in standardizing dietary supplement ingredients, particularly botanicals	X, already underway	X, Enhanced efforts	
Expedite the development and enactment of GMP's for dietary supplement manufacturers	X, already underway - proposed rule being reviewed by the Administration		

7. Finally, throughout the report, OIG should be careful as to how it characterizes FDA's role in regulating dietary supplements. For example, in many instances the OIG states that FDA does not require certain actions when it would be more appropriate to state that the applicable statute does not require such actions or provide the Agency the authority to do so. FDA has noted the instances where this has

⁵ For FOIA and Privacy Reason, FDA discourages such identification when a report is made to FDA. See MedWatch Form 3500, which request that the reporter provide only the patient's initials or some other type of identifier that will allow the reporter to readily locate the case if they are contacted for more information.

occurred, and recommends that the OIG characterize these points as what DSHEA or the Federal Food, Drug, and Cosmetic Act requires.

Technical Comments

1. FDA recommends that the Title of the OIG report be changed so that it focuses on the system and the tools FDA needs, not imply FDA inaction. For example, "FDA Needs Better Tools to Provide Adequate Safety Valve."
2. Beginning on page 1 of the Executive Summary, the report repeatedly stresses FDA's authority to seize products but does not appear to recognize the availability of other enforcement actions, such as injunctions or criminal prosecutions. The effect is to leave the reader with the impression that FDA does not have such authority under the FFDCA.
3. On page 8, the report lists dietary supplements for which private studies have shown some benefit. FDA discourages such statements, since the Agency might not have evaluated these studies.
4. In several places throughout the report, starting on page 1, the report makes distinctions between prescription drugs and OTC drugs. Though some of these distinctions are warranted, many are misleading and confusing. The most important distinction is between "new drugs" and all other types of drugs, e.g., those that are GRAS/GRAE and those whose use was subject to the Pure Food and Drugs Act of 1906. "New drugs" need to be approved under Section 505 of the FFDCA; the others do not. FDA suggests that the OIG change "prescription drugs" to "new drugs (prescription or over-the-counter)," where appropriate.
5. At several points throughout the report, beginning at page 13, OIG states that, in the NDI process, "the burden is on FDA to show why the product is unsafe." In the NDI process, we either express our reasoned disagreement with the notifier's data or arguments with respect to product's safety, or we remain silent. However, if the dietary ingredient is marketed and is, in fact, a new dietary ingredient, the issue is whether there is adequate information to provide reasonable assurance that such ingredient does not present a significant or unreasonable risk of illness or injury. See Section 402(f)(1)(B). Although the burden of proof is on FDA to show the "inadequacy" of the information, we need not show that the ingredient is "unsafe" under this standard.
6. The report (e.g., on pages 9 and 13) also suggests that the only standard for adulteration with respect to dietary supplements is found at Section 402(f)(1)(A). Inasmuch as dietary supplements are food, however, the other provisions of Section 402, the food adulteration section of the FFDCA, also apply to dietary supplements.
7. Throughout the report (beginning at page 13), statements regarding the NDI process suggest that all new dietary ingredients are subject to the process. In fact, only new dietary ingredients that were not in the food supply as an article used for food without chemical alteration require an NDI notification.
8. On page 26, the report suggests that seizures are much more broad-sweeping than they actually are. It goes without saying, almost, that FDA seizes particular lots of products or a particular manufacturer's products on a case-by-case basis. We do not generally seize all products containing a particular ingredient.
9. The report, at points, suggests that FDA does not have inspection authority over

firms manufacturing dietary supplements. In fact, FDA does have, and exercises, certain inspection authority.

10. In addition to the above, FDA has noted several technical changes in the body of the draft report. A copy of FDA's edits to the draft report is attached electronically. See Document titled "OIGdraftcomm4."



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

CONSUMER HEALTHCARE PRODUCTS ASSOCIATION

Formerly Nonprescription Drug Manufacturers Association

April 4, 2001

Michael F. Mangano
Acting Inspector General
Office of the Inspector General
Department of Health & Human Services
Washington, DC 20201

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OFFICE OF INSPECTOR
GENERAL

Dear Mr. Mangano:

Thank you for the opportunity to review and comment on the draft Inspection Report, "Adverse Event Reporting for Dietary Supplements: An Inadequate Safety Valve" prepared by the Office of the Inspector General (OIG). We recognize the importance of adverse event reporting (AER) systems and have supported better operating procedures for the current AER system in past comments to the agency.¹

The Consumer Healthcare Products Association (CHPA) is the 120-year-old trade organization representing companies involved in the manufacture, distribution, supply, advertising and research of dietary supplements and nonprescription medicines. We have been intimately involved in commenting on the evolving regulatory frameworks for both the OTC drug and dietary supplement components of the consumer self care industry. In particular, we have had a very significant involvement in both mandatory and non-mandatory AER systems in the dietary supplement and nonprescription drug industries and use this experience to provide you with detailed comments on the draft Inspection Report. However, given your short turn around time for comments, we may have additional comments as we complete our continued review of the Inspection Report.

I. Executive Summary

It is important that the Inspector General know our interest in an adequate AER system for dietary supplements. However, notwithstanding our interest in and support for adequate post-marketing surveillance of dietary supplement products, our extensive experience in this area leaves us with the conclusion that the draft Inspection Report is flawed in its approach, and is therefore of incomplete value in being a credible basis for further development of adequate and reasonable AER management within the Center for Food Safety and Applied Nutrition (CFSAN).

The core failing in the findings of the draft Inspection Report is the OIG's admission that "we do not evaluate the internal operating procedures of [CFSAN's]

¹ E.g., see CHPA's comments to Docket No. 99N-1174 pertaining to the June 8, 1999 CFSAN Stakeholder Meeting dated June 8, 1999 and August 20, 1999.

system" (page 8, last sentence). Without a completely adequate audit and evaluation of CFSAN's operating procedures for managing AERs, including CFSAN's scientific capacity to manage and evaluate the existing reports as well as CFSAN's documented procedures manuals and policies for such management, there is little support for recommendations that would result in wholesale changes to the current AER system for the subset of foods known as dietary supplements – particularly, changes that would represent requirements over and above those even required for foods or, for that matter, a very large category of nonprescription drugs.

Indeed, since CFSAN has indicated that it is seriously under-funded to effectively manage the current system, having asked Congress for two years in a row for \$2.5 million for operational development of its AER reporting system, it is premature to suggest total revamp of the current system. Rather, it would be more appropriate to determine the adequacy of the system if funding were made available.

We believe the current system can work with adequate funding to improve current operating procedures and functions as well as creation of awareness outreach programs, so that consumers and health professionals are aware of the need for, and methods to, report AERs on dietary supplements, as well as other health-related products.

As a result, CHPA asks that the Inspector General have the draft report re-evaluated before its official publication, so that its conclusions can be appropriately modified to more realistically define workable solutions to the current problems faced by CFSAN in managing AERs. Those solutions do not include a ground-up restructuring of the dietary supplement AER system in CFSAN, but rather a recognition that the current system is workable through refinements, based on increased resources for operational management and on a public education campaign relating to dietary supplements and MedWatch. We therefore recommend refinements of the current capacities of the existing system, which would keep the level of regulatory requirements consistent with those required for conventional foods, including:

1. CFSAN should develop, if it has not already done so recently, detailed operating procedures for the current AER systems.
2. CFSAN should be funded to: (a.) create and operate a state-of-the-art computer system for tracking and compiling AERs reportedly associated with dietary supplement use; (b.) manage FOI requests on AERs on a timely manner and keep the AER website updated (note: "relatedness" conclusions should not appear on the website, for the reasons given below); (c.) develop as a 2001 "A list" priority a regulatory policy framework for requiring label statements on dietary supplements, based on scientific documentation of signals in the AER system.
3. Importantly, mandatory AE reporting, registrations, and labeling requirements for toll free numbers is unnecessary as a means to have an effective safety valve in the form of an operationally-intact AER system within CFSAN, given the reasons set forth below.

*(See below for detailed comments.)***II. Detailed Comments**

In reassessing the Inspection Report, OIG should seriously consider incorporating the following points.

1. **The AER system for dietary supplements is more than just AE reports to MedWatch and is workable with improved funding.**

The AER system for consumer products, whether dietary supplements or monograph OTC drugs, is a complex system involving surveillance of the spontaneous reports as well as the published literature, poison control reports, and other information as might come to the attention of FDA, companies and health professionals. As such, the Inspection Report focuses principally on the spontaneous report component of the AER system, leading to a set of conclusions that are not only over-reaching in their specifics but also appear out of context of what is workable and achievable.

Specifically, the AER system for dietary supplements is set up to be potentially both a passive and active surveillance system, not unlike that used for OTC monograph drug ingredients. The OTC component run by CDER has identified numerous post-marketing signals on OTCs that had been marketed for many years with no indication of purported safety concerns (e.g., benzoyl peroxide, water-soluble gum, doxylamine, diphenhydramine etc.). These reports stemmed from either spontaneous AERs or from case reports or case series in the published literature. The OTC AER system has been shown to be quite sensitive to rare adverse events associated with marketed OTC ingredients (e.g., rare neosporin-related allergy), and as needed, we have stepped forward with Citizen Petitions to seek appropriate scientifically-documented labeling changes.

Similarly, CFSAN's post-marketing surveillance system for dietary supplements has picked up signals for potential problems by FDA, including Sleeping Buddha, plantain, and ephedra, among others. In the case of St. John's wort, published reports in 1999 suggested a potential for drug interactions² and a subsequent study by Piscitelli et al.³ provided the needed scientific documentation to support a labeling change, which CHPA members adopted shortly after Piscitelli's study was published. CHPA shortly thereafter petitioned the agency to adopt the CHPA voluntary labeling program on St. John's wort into regulation.

Where the OTC and dietary supplement system differ, however, is in the nature and extent of support within their respective Centers. The Center for Drug Evaluation and Research (CDER) has a separate office for post-marketing surveillance and reasonably-well worked out operational procedures for evaluating and taking action on potential signals generated by the AER system, whether pertaining to drugs covered

² Lantz, M.S. et al.: St. John's wort and antidepressant drug interactions in the elderly. *J. Geriatr. Psychiatry Neurol* 12(1):7-10, 1999. John, A. et al.: Pharmacokinetic interaction of digoxin with an herbal extract from St John's wort (*Hypericum perforatum*). *Lancet* 355(9203):547-8, 2000.

³ Piscitelli, S. C. et al.: Indinavir concentrations and St John's wort. *Lancet* 355(9203):547-8, 2000.

under New Drug Applications (NDAs) for which AER reporting is mandatory or to drugs marketed pursuant to the OTC Review, for which AER reporting is not mandatory.

CFSAN, on the other hand, does not give the same amount of resource support for AER management as CDER. There is no separate office within CFSAN for this purpose. CFSAN is unable to respond to FOI requests relating to its AER system in a timely fashion and does not keep its web-based component of its current system up-to-date. For the past two years, CFSAN has asked Congress for \$2.5 million to develop its AER system, thereby demonstrating its current critical lack of resources.

With this perspective, the recommendations of the Inspection Report appear to be over-reaching, even to the point of adding complex systems over and above anything that CFSAN could handle.

2. **It is not the failing in the current AER system for dietary supplements that has led to the relatively low number of FDA actions, but rather: (a.) the generally excellent safety profiles of many dietary supplements; (b.) FDA's only recent commitment to engage a regulatory strategy for dietary supplements; and (b.) the current lack of a clear regulatory policy to initiate labeling changes once an AER signal has been scientifically documented.**

Further to the concern expressed in the Inspection Report's about the limited number of actions taken by the agency on dietary supplements (see page 3 of report), which is used as a reason why the system should be totally changed, the Inspection Report has overlooked several clear underlying reasons for the agency's relatively low number of actions, including the following:

- a. The generally good safety profile of dietary supplements has contributed significantly to the low number of actions.

In Section 2 of the Dietary Supplement Health and Education Act of 1994 (DSHEA), Congress "identified 15 findings that were meant to establish a conceptual framework for Federal regulatory policy regarding dietary supplements."⁴ Among these findings, Congress determined that "dietary supplements are safe within a broad range of intake, and safety problems with the supplements are relatively rare."¹ Certainly, the experience since the passage of DSHEA in 1994 upholds this finding. While there have been a handful of safety issues which FDA has addressed or is in the process of addressing (e.g., the contaminant, aristolochia; characterization of the new drug GBL as a dietary supplement; Sleeping Buddha; among several others), the mainstay dietary supplement ingredients (i.e., those with the greatest exposure to the American public, such as echinacea, ginseng, garlic, ginkgo, chondroitin, glucosamine, fiber, water soluble vitamins, fat soluble vitamins, and minerals, among many others) have

⁴ Commission on Dietary Supplement Labels -- Final Report: Chapter I - Dietary Supplement Health And Education Act of 1994. Final Report Transmitted November 24, 1997.

demonstrated consistently highly acceptable safety profiles.

- b. Furthermore, one of the most important factors in contributing to the conclusion of the Inspection Report that "FDA rarely takes safety actions" over the period of January 1994 to June 2000 is the fact that it was not until March 1999 that the FDA Commissioner (i.e., Dr. Jane Henney³) acknowledged that FDA has the tools it needs to regulate dietary supplements.

Hence, the period from October 1994 (passage of DSHEA) to March 1999 was a time of little commitment within FDA to support implementation of DSHEA. Following ex-Commissioner Henney's positive acknowledgement of FDA's authority under DSHEA in March 1999, the agency spent the remainder of 1999 convening Stakeholder sessions to develop its long-range plan for dietary supplements, which was issued in January 2000. Although the level of commitment to building the regulatory framework for dietary supplements clearly changed during the period of March 1999 to June 2000 (and beyond), CFSAN was still disadvantaged by personnel turn-overs and limited resources and funding, thereby being effectively unable to use the tools it had then, and still has, to follow post-marketing safety of dietary supplements.

Therefore, we do not agree with the Inspection Report conclusions that significant gaps in the structural framework of the current AER system led to the limited actions by FDA. Rather, we conclude that there was a critical dysfunction of the agency in the 4.5 years post DSHEA followed by a very recent rallying of the agency's efforts and resources by Dr. Jane Henney and Mr. Joe Levitt, and that the needed framework is in place, only needing adequate resources.

- c. It is important to recognize that the current CFSAN administration has not set forth a policy to under-gird regulatory actions leading to mandatory labeling changes once the AER system has signaled a potential safety issue and subsequent scientific documentation has been developed to confirm the potential signal. As a result, FDA's inaction, even when it has evidence from the current AER system and support from industry, has been a result of the agency having no "end game" regulatory strategy/policy to bring closure to the findings within the AER system.

In this regard, it is important to note that for OTC monograph drugs there is a similar MedWatch-based AER system as for dietary supplements. This OTC monograph drug component of the system has also been sensitive to signals of potential safety problems, as in the reported cases of allergic reactions to neosporin, which led to a CHPA petition requesting a label warning for neosporin-containing OTC drug products, or the reported cases of choking associated with taking water soluble gums when taken with insufficient water, which also led to a CHPA-initiated label warning

³ Food and Drug Administration Commissioner Jane E. Henney, M.D. before the House Committee on Government Reform: "FDA has tools at its disposal to take enforcement actions against dietary supplements found to have safety, labeling, or other violations of the FD&C Act, as amended by DSHEA." March 25, 1999.

requirement.⁶ The significant difference between the OTC ingredient examples just named, however, and the example given above relating to St. John's wort is that FDA initiated reasonably rapidly a regulatory proceeding to act upon the scientific findings related to the OTC drug ingredients. To date, we have only been informed by FDA that the agency has not yet come to a conclusion about CHPA's Citizen Petitions relating to labeling of St. John's wort, labeling and packaging of ephedra, and labeling relating to use by pregnant and nursing women.⁷

It appears that CFSAN acknowledges this lack of scientific regulatory policy, since it lists as a "B" 2001 priority the development of guidance on "material fact" which relates to Section 201n of the Food, Drug Cosmetic Act, "failure to reveal a material fact."⁸ This should clearly be a 2001 "A" priority, rather than a "B" priority, so as to facilitate actions on our Citizen Petitions (which were developed as requested regulatory outcomes to signals in the current AER system) as well as on future findings from future signals generated by the current AER system. Indeed, the Inspection Report's failure to address this significant issue speaks to its inherent limitations as a supporting document for initiating a total revamp of the current AER system.

In summary, these three key factors need to be considered in the Inspection Report in explaining the relative low number of FDA actions on dietary supplements, so a limited perspective or bias is not presented in the Report. The generally excellent safety profiles of many dietary supplements, FDA's only recently engaged commitment to a regulatory strategy for dietary supplements, and the current absence of a regulatory policy to initiate labeling changes once an AER signal has been scientifically documented, coupled with the fact that the current system works when operationally engaged, suggests the need to refine, not totally redefine or create, the current AER system for dietary supplements.

3. The Inspection Report omits a key assessment of the effectiveness of CFSAN's AER system – a review of CFSAN's internal operating procedures.

The Inspection Report purposefully "did not evaluate the internal operating procedures of the system" (see page 1, last sentence). This is a critical omission.

The stated purpose of the report was "to assess the effectiveness of the Food and Drug Administration's (FDA) adverse event reporting system for dietary supplements in protecting the American consumer" (see "Purpose" on page 7). An assessment of the "effectiveness ... of the system" is integral to evaluating its current internal operating procedures, since such an evaluation would determine whether the gaps or shortcomings of the system were a function of processes, resources, level of staffing, inadequate

⁶ See CHPA Citizen Petitions on water-soluble gum to Docket No. 90N-0200 dated December 31, 1990, and January 4, 1991; CHPA Citizen Petition on topical antibiotics to Docket No. 95N-0062 dated June 20, 1992.

⁷ See letter from FDA to CHPA dated December 15, 2000 re Docket No. 00p-1355/CPI.

⁸ See FY 2001 CFSAN Program Priorities: "Develop guidance or regulation on safety information/material fact labeling for dietary supplements."

internal guidance, etc. – all of which in and of themselves in a system able to generate signals (see above) could be entirely adequate explanations of the Inspection Report's conclusion that the current system is an "inadequate safety valve."

To underscore this, on April 27, 1999 CHPA made a Freedom of Information (FOI) request to the agency, asking for copies of all internal procedures, manuals, policies pertaining to CFSAN's current AER system for dietary supplements, including those relating to AE case management and personnel training (copy attached). To date, we have received no detailed reply to our FOI request. In a personal follow-up with a key policy manager within CFSAN, CHPA was told that CFSAN had no such written operating procedures or training manuals.⁹ This exchange led to formal recommendations from CHPA to CFSAN to build the internal operating procedures for the current system.¹⁰ We have received no response from CFSAN on our recommendations. See the Endnote for specific CHPA recommendations on building CFSAN's internal operating procedures for its AER system.

Had the OIG investigated the internal operating procedures of CFSAN's current AER system, we believe the Inspection Report would have focused on practical improvements to the current system, as opposed to over-reaching with recommendations for mandatory AER reporting and registration, which are not required for foods (and dietary supplements are foods). Furthermore, we also believe that the Inspection Report would have identified the need for a policy framework for initiating labeling on dietary supplement products (see above), including also a warning policy, which we have proposed to the agency.¹¹

In sum, because OIG did not undertake an assessment of the operating procedures affiliated with CFSAN's AER system, we do not think the Inspection Report's conclusions are substantiated by the scope, nature, and level of "evidence" presented in the report. Without such a review, we do not see how the Inspection Report can come to meaningful conclusions and reasonable recommendations on "how well the system detects adverse event reports, generates signals of public health concerns, [and] how well FDA addresses these signals and when necessary takes appropriate actions to protect consumers."¹²

4. A public awareness campaign is a reasonably, and entirely suitable, means to address certain limitations inherent in AER surveillance systems. Placing

⁹ Personal communication from CFSAN's scientific staff member to CHPA scientific staff member.

¹⁰ See Endnote and footnote #1.

¹¹ On several occasions, CHPA has commented to FDA's Center for Food Safety and Applied Nutrition that the Center needs to articulate a clear labeling policy on when to warn. FDA has a long standing policy that has been used for consumer products, including OTC medicines and foods, which is that warnings (or decisions about product availability) should be "scientifically documented, clinically significant, and important to the safe and effective use of the product by the consumer." The importance of such a policy openly acknowledged by the Center cannot be underestimated, as it focuses public health decisions on the first hurdle, scientific documentation, as the basis for decision making. See also: 47 *Federal Register* 1982: 54754; 53 *Federal Register* 1988: 46213; and Solter, R.W.: When to Warn. *Regulatory Affairs Focus* 2 (10): October 1997.

¹² See page 8 of Inspection Report for quoted phrase.

toll free numbers on all dietary supplements labels is not.

Limitations relating to the AER system for dietary supplements are not unique to this system. In fact, even in AER systems for drug products, such as OTC monograph ingredients, there are the same limitations relating to medical, product, manufacturer, and consumer use identified in the Inspection Report. However, the lack of outreach by CFSAN, as noted in the Inspection Report, may be a significant contributor to the "statistics" quoted on pages 18-21. With a concerted effort to inform consumers and physicians about the scope, nature and extent of information needed for meaningful reports to the MedWatch system, there would undoubtedly be significant improvement in the quantity and quality of the reports. Certainly, this approach should be undertaken first, in conjunction with improved resources, before other more stringent resource-intensive approaches are proposed.

While CHPA supports efforts to enhance awareness of the AER system for dietary supplements among health professionals and consumers, we do not think that the recommendation that the FDA's telephone number be placed on the package of all dietary supplements is appropriate suggestion to addressing the current shortcomings of the system, which as noted above stem principally from a weak policy structure and resource limitations. Aside from the fact that mandatory labeling of toll free numbers is not required for drugs or other foods, it is also troubling to consider how FDA would manage the sheer volume of calls relating to non-serious and serious AERs as well as general consumer inquiries. Companies use toll free numbers on their labeling as much for consumer outreach and product development as for the management of validated serious AERs to their products. Only a subset of information relates to serious AERs, which is that cadre of AERs about which FDA and industry would be most interested from a safety standpoint. Expecting a consumer to evaluate seriousness vs. non-seriousness prior to using a toll free number on a label is simply unrealistic. Further, one toll free number on all products would likely detract from the use of local poison control numbers. The handling accidental overdose-related 24-hour emergency calls would also over-burden an FDA-managed AER system, and create a redundancy to the current national poison control system. Hence, mandatory labeling with a toll free number, while perhaps on the surface an attractive option, is on further in-depth reflection open to serious limitations and objections.

5. **"Relatedness" of AERs should only be evaluated and used in the context of a dialogue among qualified experts, as a means to generate hypotheses about ingredient safety or in recommending formal public health actions.**

The assertion in the Inspection Report that public disclosure of "relatedness" of the AER profile would be a useful form of risk management is a serious shortcoming (i.e., see pages 21 and 30), as noted in the following points:

- The consumer is unprepared to make a scientific judgement about anecdotal reports.

- AERs are by definition anecdotal and except in certain very highly selected circumstances for the most part useful only for hypothesis generating, requiring follow-up clinical or epidemiologic studies, as indicated elsewhere in the Inspection Report.
- Given the commentary in the Inspection Report that much information is missing from the AER, there is the very real likelihood that “relatedness” conclusions would be errors in judgement – either falsely implicating a product with a particular safety endpoint or, by contrast, falsely implying that the product is not related to the safety endpoint.
- Invariably “relatedness” judgements are inherently subjective, irrespective of how structured the process attempts to be; hence it is open to reviewer bias.

Thus, “relatedness” conclusions about AERs should be used only in scientific discussions about the safety of the ingredient/product (i.e., whether a drug, dietary supplement, conventional food, or cosmetic) or device by experts qualified in epidemiology, post-marketing surveillance and epidemiology. They should not appear on FDA’s website, which is tardy in its updates and where incomplete information can be the difference between “possibly related” (which would be interpreted by the uninformed consumer as “related”) and “not related.”

In sum, the Inspection Report fails to recognize that possible or probable “relatedness” is interpreted as definite “causality” by the consumer. Posting “relatedness” ratings without due process of scientific investigation to adequately document scientifically the purported relationship between a dietary supplement and a reported adverse event amounts to regulation by fiat. This is not how the science of self care consumer products, whether dietary supplements or OTC drugs, should progress.

Summary Recommendations

In summary, a more reasonable approach to addressing the effectiveness of the current AER system for dietary supplements would be to refine the current capacities of the existing system, which would keep the level of regulatory requirements consistent with those required for conventional foods. Indeed, because of the lack of demonstrated commitment to implementing DSEHA until relatively recently, the apparent lack of defined operating procedures and policies for the current AER system, and the known ability of the current system to signal potential safety problems, we are led to the following three recommendations:

1. CFSAN should develop, if it has not already done so recently, detailed operating procedures for the current AER systems. As stated, for the first 4.5 years after the passage of DSHEA there were apparently no such procedures, highlighting the importance of assessing FDA’s operating procedures as a basis for evaluating the effectiveness of the current system.

2. CFSAN should be given the funds and resources to: (a.) create and operate a state-of-the-art computer system for tracking and compiling AERs reportedly associated with dietary supplement use; (b.) manage FOI requests on AERs on a timely manner and keep the AER website updated. "Relatedness" conclusions should not appear on the website for the reasons given above; (c.) develop as a 2001 "A list" priority a regulatory policy framework for requiring label statements on dietary supplements, based on scientific documentation of signals in the AER system.
3. Importantly, mandatory AE reporting, registrations, and labeling requirements for toll free numbers is unnecessary as a means to have an effective safety valve in the form of an operationally-intact AER system within CFSAN.

In closing, feel free to contact me, should you wish clarification or follow-up to our remarks. Given that you provided us with a very short turn-around for reading the draft report, developing comments and obtaining member comments, we continue to review the report and may have additional comments in the future.

Sincerely yours,



R. William Soller, Ph.D.
Senior Vice President and
Director of Science & Technology

cc: J. Levitt
C. Lewis, Ph.D.,

ENDNOTE

Excerpted from Page 4 of CHPA's Comments to Docket No. 99N-1174 pertaining to CFSAN's June 8, 1999 Stakeholder Meeting:

"Therefore, as stated in its May 27, 1999 comments to the House Committee on Government Reform, CHPA recommends:

- a. "CFSAN prepare a written plan for and adopt a systems approach, similar to that recommended in FDA's May 1999 document "Managing the Risks from Medical Product Use: Creating a Risk Management Framework" to the management of AERs on dietary supplements, grounding this approach in the agency's current safety policy (i.e., "warnings, or discussions on product availability, should be scientifically documented, clinically significant and important to the safe and effective use of the product by the consumer");

- b. "CFSAN should keep current written protocols for CFSAN personnel handling AERs to expedite accurate data collection, including a detailed decision tree for use by those whose responsibility it is to filter serious and non-serious reports and route these reports for expeditious follow-up;
- c. "CFSAN should have a policy and procedures for timely sharing of serious AERs with affected companies, in order to help facilitate adequate follow-up and so address incompleteness and inaccuracies in AE reports;
- d. "Specific CFSAN training manuals and procedures should be established to ensure quality collection, analysis and reporting of AERs;
- e. "CFSAN should undertake a review of the core competency of the personnel who would operate different facets of an adequate AER system on dietary supplements;
- f. "A re-engineering of the public access to AERs for dietary supplements is needed. AERs should be available to the public in a timely fashion when FDA (a.) has communicated with the affected company identified in the AER and (b.) is prepared to provide publicly a complete file of the report omitting confidential information. "A specific "causality assessment" should not be applied to each AER received by FDA, since causality cannot be established for most AERs by virtue of their retrospective nature and the fact that the overall strength of the reported association, which seeks to define likelihood of a reported association, encompasses much more information and data than just one or a few AERs.
- g. "Public input is needed in the development of policies and procedures to be used in CFSAN's systems approach to AER management."

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April 6, 2001

VIA EMAIL AND REGULAR MAIL

Mr. Michael F. Mangano
Acting Inspector General
Department of Health and Human Services
Washington, DC 20001

Re: Draft Report: Adverse Event Reporting for Dietary Supplements:
An Inadequate Safety Valve; OE1-01-00-00180

Dear Mr. Mangano:

Thank you for providing the American Herbal Products Association (AHPA) the opportunity to review the Office of the Inspector General (Office) Draft report regarding adverse event reporting for dietary supplements. AHPA is the national trade association and voice of the herbal products industry. AHPA is comprised of domestic and foreign companies doing business as importers, growers, processors, manufacturers, marketers, and distributors of herbs and herbal products. AHPA serves its members by promoting the responsible commerce of products that contain herbs and that are used to enhance health and quality of life.

We have substantial comments on the Draft and its recommendations which, we believe, is crafted as a general criticism of the Dietary Supplement Health and Education Act of 1994 (DSHEA) and not as any kind of reasonable evaluation of the Food and Drug Administration's (FDA's) adverse event reporting (AER) system for dietary supplements. Indeed, we were shocked to see that despite the Draft's stated purpose "To assess the effectiveness of the FDA's adverse event reporting system for dietary supplements in protecting the American consumer," that the Office's inquiry "did not evaluate the internal

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Mr. Michael F. Mangano
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operating procedures of the system." Instead, the report criticizes a regulatory system which was enacted with no dissenting votes in either the House or the Senate and signed into law only six and one-half years ago by President Clinton without any adverse comment.

In our comments, we address the points made in the body of the Draft in the order in which they appear. We have not attempted to restate every point made in the Draft and instead have focused on being responsive to the Office's request for comments. We would be pleased to meet with the Office staff to further discuss and communicate the serious concerns that AHPA has with the Draft, its tone and its direction. In our view, a dialog is important to assuring that all concerned are fully informed of the issues and the respective positions of the parties.

THE SO-CALLED UNIQUE ROLL OF THE ADVERSE EVENT REPORTING SYSTEM FOR DIETARY SUPPLEMENTS.

The Draft concludes that that the Adverse Event Reporting (AER) system for dietary supplements plays a unique roll. First, the Draft states that "FDA has relatively little clinical data on ingredients and that this is an inherent limitation in its ability to investigate adverse event signals generated by its AER system." This results, according to the Draft, because FDA does not require the submission of safety data prior to the marketing of dietary supplements. This is the law for old dietary ingredients. And while the Draft recognizes that premarketing submission of safety information is required for new dietary ingredients, it criticizes this system because FDA does not have documentation with respect to whether particular dietary ingredients are new or old. The Draft then notes that the burden of proof is on the FDA to demonstrate that a dietary supplement is unsafe or adulterated before it can take regulatory action.

The last point about burden of proof should be removed. The United States always has the burden to prove a violation of law before it may take regulatory action. Our system of justice does not allow government agencies to declare guilt and then demand proof of innocence. FDA also has the burden of proof with respect to prescription drugs once they have been approved for marketing. Congress determined that dietary supplements do not require premarket approval and that the government must meet its burden of proof if it wishes to act against such products. There is nothing novel or unique about this provision and the public policy it effectuates.

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In making the statements about a lack of premarket safety information, the Draft wholly ignores the history of use associated with dietary supplement ingredients and the realities of marketing a consumer product in the United States. First, FDA and anyone else can find information regarding most dietary ingredients by searching the scientific literature that is available on Medline and through other research data bases. There is substantial research available regarding the safety and utility of vitamins and minerals. Similarly, there is a rich history regarding the traditional use of herbs. In this literature, the authors do not fail to note any side effects that may have been observed with respect to any particular herb. This rich literature forms the basis of AHPA's *Botanical Safety Handbook* which was published in 1997 to provide safety information regarding botanicals.

Second, the Draft seems to take the position that unless there is a Federal system requiring premarket approval and clinical testing of a product, no substantiation of its safety for use will be made prior to marketing. This ignores the history of use and scientific research available for most such products. The common law of product liability requires that a product be safe for its intended use and the common law is not a complex regulatory scheme. The Draft also seems to state that dietary supplements are somehow different from other products because they may be determined to be safe even if someone suffers an adverse event while taking more than the recommended dose is surprising because that is plainly how prescription drugs, over-the-counter drugs and other products are viewed by the law. Paracelsus' axiom that "the right dose differentiates a poison from a remedy" applies equally to foods, drugs and dietary supplements. And the concept that labeled doses or serving sizes are legitimate ways to address this issue is fundamental and well established.

That there are risks associated with some dietary supplements, as the Draft points out, is evidence only that a functioning AER system is important, not that DSHEA needs to be amended or that a complex regulatory scheme like that recommended in the Draft is necessary. The Draft points out effects of vitamin A (fetal risk) and ginkgo (blood thinning) that are well known. As a result of that knowledge, the dosage of vitamin A in dietary supplements is limited. And with respect to ginkgo, its potential for blood thinning is of greatest concern for those who are taking the prescription drug warfarin, a drug that already cautions prescribers to carefully monitor patients and specifically discusses ginkgo. With respect to prescription drug interactions, the FDA's Medwatch system for prescription drugs will pick up the presence of concomitant use dietary supplements in patients reported through that system because concomitant

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therapy is one of the items on the Medwatch reporting form. Accordingly, this issue is being addressed.

The two instances of product contamination noted in the Draft are old news. The L-tryptophan situation was history when DSHEA was passed in 1994 and it was one of the reasons Congress provided FDA with authority to promulgate current Good Manufacturing Practice regulations, a draft of which was promptly provided in 1995 to FDA by AHPA and three other industry trade associations. The FDA's own cGMP proposal has yet to issue. The plantain contamination situation was discovered when FDA scientists acted as public health detectives and determined that the this herb had been contaminated with the pharmaceutical herb, digitalis lanata. Once this was determined, members of the herbal products industry stopped selling plantain until its integrity could be restored.

AHPA shares the concern expressed in the Draft that some dietary supplements may not bear appropriate warnings or cautions. AHPA published the Botanical Safety Handbook to encourage the provision and evaluation of such information. And it has published various Trade Recommendations which also address this subject for particular herbs (e.g., ephedra) and for classes of herbs (those that should not be used during pregnancy or while nursing).

Similarly, AHPA is the publisher of *Herbs of Commerce* that FDA has adopted with respect to the common names of herbs. Contrary to the Draft, there are not multiple common names for ephedra. The basic ephedra herbs, those found mainly in Asia, are known as ephedra. Other species, for example those found in the American Southwest, are called by other names including Mormon tea. There are also "other common names" that appear for ephedra in *Herbs of Commerce* so that they may be cross-referenced to ephedra. AHPA shares the concern expressed in the Draft that FDA may not be adequately enforcing labeling requirements and regulations for dietary supplements. But this discussion, in the context of the Draft, has nothing to do with the successful operation of FDA's AER system. If products are labeled unlawfully, FDA has laboratories to detect their true content.

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FDA'S AER SYSTEM DETECTS RELATIVELY FEW ADVERSE EVENTS

The Draft's conclusion that the FDA's AER system detects relatively few adverse events associated with dietary supplements proceeds from unfounded comparisons to Poison Control Centers and to the Texas Department of Health. Poison Control Centers have a different definition of adverse event and the Texas State Department of Health reports referred to in the Draft resulted in the main by a Texas Department of Health's call upon the public to advise them of any adverse events associated with certain ephedra-based weight loss products, thereby providing a database that is not comparable to FDA's.

The rationale of the Draft to justify the underreporting conclusion could just as easily be a rationale to support substantial reporting. That consumers may believe dietary supplements are safe is a reason why reports would be made if side effects are experienced. That supplements are self-care products is also not a reason for underreporting. Indeed, the Draft does not provide a rationale for why this may be so, and instead seems to say that the lack of the involvement of health professionals provides some basis for this assertion. It does not. Finally, the perceived lack of Federal regulation of supplements, whether it evolves from the disclaimer on supplement labels or the fact that the FDA does not visibly enforce the laws and its own regulations, does not mean that consumers would not make adverse events known if they were to occur. In this litigious society, where advertisements by "victim's rights lawyers" blanket the media, it is totally without basis to suggest that consumers would not find someone to report to if they believed a product has caused them harm.

AHPA agrees that FDA performs little outreach to consumers with respect to the reporting of adverse events associated with dietary supplements. But this is also true with respect to outreach to consumers of prescription drugs, over-the-counter drugs, medical devices, cosmetics and food. FDA does perform some outreach to health care professionals to make such reports for very good and obvious reasons. Such professionals are more likely to report the important information set forth in the Draft and to note the presence of other factors that might impact the reported event.

There is no reason why FDA should single out dietary supplements for special AER outreach treatment. Moreover, there is something inherently wrong about the concept of a United States government agency encouraging the public

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to complain about a particular class of products. We do not believe this kind of outreach is performed by any government agency .

FDA'S AER SYSTEM AND THE GENERATION OF PUBLIC HEALTH SIGNALS

In this section of the Draft, the Office bemoans the lack of detailed information that FDA was able to gather on the AER reports it designated for follow-up. For example, consumers sometimes do not authorize the release of their medical records. But this is true for all of the products regulated by FDA, there is nothing special about dietary supplements that would or should make access to patient medical records different. Similarly the Draft reports that FDA was unable to determine the ingredients for almost one-third of the AER reports it received. Because of this, the Office recommends that all supplement manufacturers register their products and list their ingredients, something that is not required for foods, the larger class within which supplements fall. And this recommendation comes even though the Federal Food, Drug, and Cosmetic Act has since 1938 required that the name and city of the manufacturer or distributor to appear on the label of foods, drugs, cosmetics and medical devices. The fact that FDA could not locate manufacturers or distributors in a few instances is not a reason to create registration requirements that FDA would not, in any event, have the staff to process and utilize. The short answer to the problem described in the Draft is for FDA to work harder to get the information it seeks and to enforce the laws on the books, not to create a new regulatory scheme.

While AHPA has consistently supported the proposal by FDA of current Good Manufacturing Practice regulations for dietary supplements, AHPA disagrees that their promulgation would assist FDA in acquiring ingredient information for dietary supplements. This information is presently required on labels and FDA should be able to ascertain whether a product meets label claims, as required by the present law and regulations, without reference to another regulatory layer.

The Draft also expresses concern that FDA does not receive many reports of adverse events from manufacturers. This should not be a surprise. FDA only receives substantial numbers of such reports from those regulated sectors where companies are required by law to make such reports. Thus, FDA requires such reports from manufacturers and distributors of prescription drugs and certain medical devices. Such reports are not required for foods, cosmetics or over-the-counter drugs. There is no basis to impose such a requirement on dietary

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supplements when sectors of the FDA regulated community whose products affect more consumers than dietary supplements have no such requirement.

The fact that there is limited contact information from consumers making reports on dietary supplements is as easily related to the reporter's own lack of concern about the report they make than a concern over privacy. FDA makes clear to AER reporters that the agency does not share personal information with anyone outside the agency. To assume that consumers ignore this advice out of a concern for privacy is simply fantasy. Where FDA is not able to obtain more information about a report, it should say so in the file. "Lost to follow-up" is important information to those evaluating such reports because it bears on the seriousness and substantiality of such reports.

FDA's computer database of AER reports for dietary supplements does in fact allow tracking and analysis of trends. It is in this section that the Draft identifies the main problem with the database, a lack of personnel at FDA to enter the information into the system. Finally, the Office should consider whether the allegedly small number of reports received by FDA is not a problem of the system but a reflection of the lack of substantial safety issues with this product class.

FDA LACK OF INFORMATION TO ASSESS POSSIBLE AER SYSTEM SIGNALS

The Draft strays far from the mark when it argues that the lack of premarket approval information for dietary supplements is a reason that FDA is allegedly not able to assess signals given by the AER's received. As stated at the outset, there is substantial information available in the scientific literature regarding dietary ingredients. Signals received can be compared to what is reported in the literature.

Information on consumer use of dietary supplements is available from private sales tracking companies. This information can be purchased by FDA from such organizations and to do so would be a more cost effective way of obtaining sales information than any regulatory requirement that it be provided by manufacturers to the government. AHPA notes that mandatory submission of product sales is not required for foods, cosmetics, most medical devices or for over-the-counter drugs.

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FDA RARELY TAKES SAFETY ACTIONS RELATED TO AER REPORTS

The Draft describes various safety actions taken by FDA based on AER reports and other information. The Draft's conclusion is that simple public disclosure of product risks and of violative products is an ineffective tool to assure that unsafe products are controlled. The Draft reaches this conclusion despite the recognition that the dietary supplement industry responsibly addressed the plaitain contamination situation when it arose. AHPA agrees, however, with the Draft that FDA needs to take enforcement action where simple publicity and discussions with manufacturers are not effective in protecting the public health. FDA has taken little enforcement action with respect to dietary supplements. Industry has urged FDA to take such action where it is warranted. FDA will not have the respect of consumers or the regulated community until it does so.

RECOMMENDATIONS

AHPA addresses each of the Draft's Recommendations below.

RECOMMENDATION 1: Facilltate greater detection of adverse events.

Require dietary supplement manufacturers to report adverse events to FDA.

This recommendation would place dietary supplements in the same regulatory posture as prescription drugs and certain medical devices. Neither the Draft nor any other information available to AHPA provides any justification for such a requirement. Not only is such a system not justified, FDA plainly does not have adequate resources to implement such a system. Until the present AER system is made operative and evaluated, any suggestion of a mandatory system is wholly premature.

Contract with Poison Control Centers to obtain their adverse event reports on dietary supplements.

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The evaluation by FDA of Poison Control Center information utilizes existing information and may be a cost-effective means of enhancing the available body of information about dietary supplements.

Inform health professionals and consumers about the adverse event reporting system for dietary supplements.

A campaign to have health care professionals and consumers report dietary supplement adverse events to FDA would be unprecedented. FDA presently makes information about adverse event reporting available on its website. Nothing further should be done in this regard.

The suggestion that companies be required to put an 800 number on their products is extraordinary. We are not aware of any substantial class of consumer products where there is such a requirement. It is not required for foods, cosmetics, drugs, medical devices or pesticides. To single out dietary supplements for such a requirement is wholly unjustified.

RECOMMENDATION 2: Obtain more information on adverse event reports in order to generate stronger signals of public health concern.

Educate health professionals about the importance of including medical information in adverse event reports.

AHPA agrees with this recommendation as it pertains to FDA's Medwatch system in general. Health care professionals should be educated to provide detailed medical information in adverse event reports.

Require dietary supplement manufacturers to register their products with FDA.

AHPA disagrees with the recommendation that all dietary supplement manufacturers register their products with FDA. Ingredients are listed on product labels as required by existing law. No special system is necessary to accumulate this information at FDA.

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Notify manufacturers when FDA receives an adverse event report.

AHPA does not agree that FDA should notify manufacturers when an adverse event report is received on a product. AHPA's position is that FDA should keep its database up to date. If the AER report database is available on FDA's website, manufacturers that choose to obtain reports regarding their products can do so. The FDA ought not to be sending such reports to manufacturers without a request because manufacturers or distributors would not be able to follow-up on such reports due to the lack of identifying information in the redacted versions of the reports that FDA makes public.

Require dietary supplement manufacturers to register with FDA.

The Draft's recommendation that manufacturers be required to register with FDA is not justified. Federal law has required manufacturer or distributor information to appear on the product labels since 1938. FDA ought to assure this information is accurate by enforcing this requirement.

Emphasize to health professionals and consumers the importance of providing a way to identify the alleged injured party.

As stated previously, this recommendation for consumer identification should be applied to all product categories at FDA. Accordingly, this advice should be given through the Medwatch system generally.

Develop a new computer database to track and analyze adverse event reports.

AHPA agrees that FDA should utilize and improve its database and tracking system for dietary supplement AERs.

RECOMMENDATION 3: Obtain vital information to adequately assess signals generated by the adverse event reporting system.

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Issue guidance on the type of safety information that manufacturers should include in the 75-day premarket notification requirement for new dietary supplement ingredients.

AHPA does not believe this recommendation has anything to do with the subject matter of the Draft. It should be removed from the Draft. FDA is presently reviewing 75-day premarket notifications and that experience will teach all concerned whether more substantial guidelines on data requirements are appropriate.

Explore the possibility of a monograph system for dietary supplements that would contain safety information on particular ingredients.

The suggestion of a monograph system for dietary supplements is wholly outside the subject matter of the Draft. This recommendation should be removed. FDA is presently addressing this possibility and the matter can be evaluated after FDA has done its job. A monograph system for over-the-counter drugs was begun thirty years ago and many of the various drug categories first addressed in the 1970s (including internal analgesics such as aspirin) have not become final. No monograph system for any type of product should be started that cannot, in a reasonable period of time, be brought to closure.

Collaborate with the National Institutes of Health in setting a research agenda addressing safety issues.

AHPA does not believe this is an appropriate subject of this Draft but agrees NIH and FDA should work together to establish a dietary supplement research agenda. AHPA respectfully suggests that the industry and consumers be included in those discussions.

Assist industry and the United States Pharmacopeia in standardizing dietary supplement ingredients, particularly botanicals.

AHPA does not believe that this recommendation is an appropriate subject of this Draft. The subject of standardized ingredients,

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particularly botanical ingredients, is complex and has nothing to do with FDA's AER system for dietary supplements.

Expedite the development and enactment of good manufacturing practices for dietary supplement manufacturers.

AHPA agrees and has consistently urged that cGMPs for dietary supplements be proposed. Nonetheless, such a proposal has nothing to do with an AER system for dietary supplements.

RECOMMENDATION 4: Disclose more useful information to the public about dietary supplement adverse events.

AHPA disagrees with this recommendation insofar as it would have FDA reach conclusions about the likelihood of whether a product or ingredient may or may not be associated with the adverse event. This smacks of a causation finding and any such information might be deemed a government document and perhaps allowed into evidence in litigation. It is for this reason and the fact that FDA will not make its personnel available for examination in litigation that these kinds of conclusions are rarely made by FDA. If FDA cannot be questioned about such findings, whatever they might be, such findings can deprive one party or the other of the right to have the matter resolved fairly in litigation without the prejudice of an FDA finding. This is the case for prescription drugs and other products regulated by FDA. Dietary supplements should not be treated differently.

As stated at the outset of this letter, AHPA would be pleased to meet with Office staff to discuss the Draft at any time.

Sincerely yours,

Anthony L. Young
General Counsel
American Herbal Products Association

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APPENDIX C

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cc: Michael McGuffin
President
American Herbal Products Association

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April 6, 2001

Michael F. Mangano, Acting Inspector General
HHS Office of Inspector General
Room 5246 Cohen Building
330 Independence Avenue, S.W.
Washington, D.C. 20201

Dear Mr. Mangano:

The Council for Responsible Nutrition (CRN) appreciates the opportunity to provide comments on the draft report of the IG on adverse event reporting for dietary supplements. This opportunity seems especially critical to us, in that we see a number of serious problems and even errors of fact in the report as it now stands.

CRN is a trade association representing about 110 manufacturers of dietary supplement products. Our members are committed to providing consumers with safe and beneficial dietary supplements manufactured to high quality standards. We recognize the importance of an adverse event reporting system that provides regulators and the industry with signals alerting them to the existence of potential problems with any consumer product. This is especially important with regard to products that are ingested, including conventional foods, dietary supplements, and pharmaceutical products. We have worked with the Food and Drug Administration on issues relating to the safety of dietary supplements for many years, and have made recommendations to the agency and to Congressional committees regarding improvements needed in the adverse event reporting system. We recognize several of our suggestions in some of the recommendations that are already covered in the IG's report. CRN worked with the appropriations committees in the last Congress to build support for the additional funds FDA needs to improve its handling of adverse event reports, with some success.

While CRN recognizes the need for an effective adverse event reporting system, we also strongly believe the approach to collecting and evaluating such reports relating to dietary supplements should be viewed in the context of other food-related systems. We are extremely troubled by the view repeatedly expressed in the IG's report that the appropriate comparison is to prescription drug reporting systems. This is entirely inappropriate. The correct comparison is to the systems currently in place for other self-selected consumable products, including foods such as medical foods and infant formula, as well as OTC drugs.

We are equally concerned about the negative view of dietary supplements that we believe pervades the IG's report. The popularity of dietary supplements and the belief that they are generally safe are viewed as risk factors, rather than as evidence that the vast majority of products are indeed both beneficial and benign. We believe in this respect the IG's report represents a failure to fairly evaluate the product category.

Because dietary supplements are not subject to a requirement for premarket approval based on proprietary research submitted by the manufacturer, the IG's report concludes that there is little scientific basis for the purported benefits of these products. This is an entirely false assumption. In fact it is the abundance of publicly available scientific research that drives both the manufacturers' and the consumers' interest in dietary supplements, and this needs to be fully acknowledged in the report.

The report paints a negative picture of the dietary supplement industry, implying that many companies are fly-by-night operations that FDA has difficulty locating. In fact, the vast majority of dietary supplements are manufactured by large corporations that are well known to the agency since they are regularly inspected. *Nutrition Business Journal* estimates that the largest 65 manufacturers in the business account for about 75% of the products on the market. The products these companies make are properly labeled, as required by regulations, but unfortunately labels are not routinely submitted by individuals reporting an adverse event. The report indicates that FDA lacks a product label in 77% of the adverse event reports in the database, but fails to make the point that the lack of a label may largely explain the agency's difficulty in tracking products.

These general concerns will be reflected in many of our specific comments, keyed to specific page numbers in the IG's report. The specific comments are attached.

CRN and its member companies are very hopeful that our comments will be taken seriously and will result in significant changes in the overall tone and content of the IG's draft report on adverse event reporting for dietary supplements. We believe extensive changes are essential, before the report is made public, and we would welcome the opportunity to review the next draft before a decision is made to release it. The faults in the present draft are so severe that we believe releasing it in its current form would be a major disservice to the dietary supplement industry and could impede rather than advance productive discussion of the important issue of improving the adverse event reporting system for dietary supplement products. We are prepared to work with the IG's office in any way possible to provide the information necessary to support vitally needed improvements in the current draft.

Sincerely,

Annette Dickinson, Ph.D.
Vice President, Scientific and Regulatory Affairs

**INSPECTOR-GENERAL'S REPORT ON ADVERSE EVENT REPORTING
FOR DIETARY SUPPLEMENTS**

**COMMENTS SUBMITTED BY
THE COUNCIL FOR RESPONSIBLE NUTRITION
APRIL 6, 2001**

EXECUTIVE SUMMARY

Page 1, end of "background" paragraph

This paragraph notes that "unlike prescription drugs, FDA does not require supplements to undergo premarket approval for safety and efficacy. Instead it relies mostly on its adverse event reporting system to identify safety problems." This statement is the first of many instances in which the prescription drug reporting system is taken as the appropriate comparison category for dietary supplements. CRN believes this comparison is inappropriate. At the least, the IG should add an additional statement such as: "FDA also relies on adverse event reporting to identify and quantify potential safety problems in food products including medical foods and infant formula. FDA also has periodically imposed specific reporting requirements to ensure adequate monitoring of some food ingredients. This was the case in the past with sulfites and aspartame, and is currently being required for products containing olestra."

Page 2, paragraph on "limited product information"

The final sentence of this paragraph states: "Product samples are especially helpful because dietary supplement ingredients are not standardized." This is a curious statement. Product samples are always helpful, even with foods or standardized pharmaceutical products, because adverse events can be due to errors in formulation or accidental contamination. The value of product samples accompanying any adverse event report has nothing to do with whether ingredients are "standardized."

Page 2, paragraph on "limited manufacturer information"

This paragraph states that FDA receives 90 percent of adverse event reports about prescription drugs from their manufacturers. It should also acknowledge that the reason for this is that prescription drug manufacturers are subject to a mandatory reporting requirement. There is no mandatory reporting requirement for adverse events associated with OTC drugs or with foods, including medical foods and infant formula. This should also be acknowledged.

Page 3, paragraph on "limited clinical information"

This paragraph says there is little clinical research on the safety and efficacy of supplements, because premarket clearance is not required. This is a false statement. In fact, there is an abundance of clinical research on the safety and efficacy of supplements, ranging from vitamins and minerals to omega-3 fatty acids to botanical ingredients. Indeed, it is the existence of this rich and ever-expanding scientific research base that drives marketers to provide ingredients such as these in the form of dietary supplements. It is this abundant and publicly available database that provides the foundation of both the consumer and the commercial interest in the product category.

Page 3, paragraph on "limited information on consumer use"

This paragraph suggests that it is essential that FDA have a mechanism for tracking the number of consumers using a particular supplement, in order to determine the incidence and seriousness of adverse events. In fact, it is not always necessary to know the denominator of consumer usage in order to justify action based on safety concerns. One example cited in the IG's report is the plantain warning and product recall, based initially on a single adverse event report due to a misidentified ingredient, namely a variety of digitalis instead of the intended ingredient plantain.

Page 3, heading asserting that FDA "rarely takes safety actions" based on adverse event reports

This heading is not supported by the text, which in fact says that FDA took 31 actions between January 1994 and June 2000. This number of actions cannot be characterized as "rare" events. The fact is that most dietary supplements have a broad range of safe intakes and the number of products presenting a significant safety concern is small. This in itself explains to a large extent why numerous actions are not required or taken by FDA.

RECOMMENDATIONS

Page 4, recommendation 1

The IG's first recommendation is that manufacturers of dietary supplements should be required to report adverse events to FDA. The paragraph notes that such reporting is currently mandatory for pharmaceutical products marketed under a new drug application. Again, the IG's report proceeds on the assumption that the appropriate comparison is between dietary supplements and prescription drugs. This is not the case. It should be acknowledged that mandatory reporting is currently not required for OTC monographed drugs or for conventional foods, including medical foods and infant formula. As the report stands, it is made to appear that only dietary supplements are free of the requirement for mandatory reporting, and this is not correct.

It is CRN's belief that a potential requirement to report serious adverse events is an issue that bears further discussion. CRN would be opposed, however, to a general requirement to report all events, including minor effects. In order to facilitate further discussion, further definition of serious adverse events -- and even of adverse events *per se* -- will be needed. For example, adverse events need to be distinguished from simple product complaints, such as complaints about taste or color, even recognizing that changes in organoleptic qualities of a product may sometimes be an indicator of a potential safety issue. Also, serious events need to be distinguished from minor events. CRN and other industry trade associations are currently reviewing proposals from third-party organizations that could provide services relating to collecting and evaluating serious adverse event reports.

The third part of the first recommendation is that an FDA phone number should appear on all dietary supplement labels. It should be noted that there is no such requirement for any other consumer product category, including OTC drugs and prescription drugs. It is CRN's belief that there is no basis for imposing any such requirement uniquely on dietary supplement products. Many dietary supplement manufacturers currently provide an 800 number to facilitate consumer inquiries, including reports of adverse events. CRN believes providing an 800 number is a commendable company policy which should be encouraged.

Pages 4 and 5, recommendation 2

It is suggested that dietary supplement manufacturers be required to register with FDA, and that individual products should also be registered. This is a suggestion that bears further discussion, provided the topic is simple registration and not the precursor of a cumbersome registration or licensing system such as exists in some countries.

It should also be noted that FDA currently has a vast amount of information available on dietary supplement manufacturers and products, since the agency has in the past several years received thousands of notifications from hundreds of companies regarding structure/function statements used in labeling, as required by DSHEA. These notifications have been compiled in a database made available commercially by AAC Consulting, and that database provides a valuable source for cross-referencing many products and manufacturers.

The IG's report also suggests that FDA should notify manufacturers upon receipt of an adverse event report, to alert the company and to obtain more product information. CRN has suggested this, in comments submitted to FDA on program priorities and in testimony presented in Congressional hearings. We believe it deserves serious consideration. The company would then be in a position to provide important information on the actual formulation of the product as well as substantive data relating to any potential safety concerns.

It is suggested that FDA develop an improved computer database for tracking and analyzing adverse events. CRN has also suggested this in the past, and we worked with

appropriations committees in the last Congress for additional FDA appropriations for this purpose, with some success.

Page 5, recommendation 3

The IG's report suggests that FDA issue guidance on the type of safety information needed in a 75-day notice. Several industry members have supported the need for additional guidance in this area, and CRN believes guidance could be helpful, provided the guidance does not result in creating a burden equivalent to the current food additive approval system.

The report suggests that a set of monographs be developed on the safety and benefits of dietary supplements. CRN believes this is a good idea, in concept, provided a drug standard of proof is not applied and providing the monograph is not taken as the equivalent of a preapproval system such as the one that exists for OTC monographed drugs.

In the Nutrition Labeling and Education Act, it was recognized that health claims for foods do not need to be based on a drug-like level of proof. For example, foods are not typically subject to the type of controlled trials that are undertaken for drugs. However, epidemiological data regarding healthful dietary patterns in large populations can provide the basis for scientifically sound public recommendations as well as health claims relating to the importance of certain nutrients or types of foods. In other cases, there may be substantial clinical data regarding the effects of some specific nutrients or food components, as in the case of the role of calcium in reducing the risk of osteoporosis. The food model rather than the drug model should be utilized in evaluating dietary supplements, if and when monographs are developed.

It is noteworthy that FDA has already contracted with IOM (Institute of Medicine) for the development of monograph concepts relating to the safety of dietary supplements, and the Research-Based Dietary Ingredient Association has likewise contracted with LSRO (Life Sciences Research Office) for a set of monographs on the safety and benefits of certain ingredients used both in dietary supplements and in functional foods. Thus, the value of third-party reviews of dietary supplement safety and benefits is a concept which is being recognized both by industry and by the agency.

The IG report suggests that FDA collaborate with NIH in setting a research agenda including dietary supplement safety issues. This is an excellent idea and is already to some extent ongoing.

The report suggests that the industry and USP should standardize dietary supplement ingredients, particularly botanicals. It is unclear in this context what the IG envisions by the term "standardization." Dietary supplements are formulated to meet the health needs and preferences of a wide variety of people. Even in the vitamin area, ingredients and formulations are not "standardized," and there is a demand for products ranging from multivitamins to single nutrients, and from low potencies (only a fraction of the RDI) to

high levels of some nutrients (vitamin E at 400 IU, vitamin C at 1000 mg). In the botanical arena, there could be a legitimate purpose served by products providing different levels of intake or different combinations of ingredients. CRN does not believe there is a need to "standardize" all ingredients and products. However, it may well be desirable to define certain terms used in product labeling to improve consumer understanding of products that are "standardized" to contain a certain percent of an active ingredient, for example.

The IG's report recommends that FDA expedite the development of GMPs. It should be noted that the industry fully supports GMPs, has worked diligently to provide FDA with a model for dietary supplement GMPs, and is anxious to see appropriate GMPs finalized. Also, most of the industry associations have already committed that their members are observing the GMPs set forth in the initial FDA publication in 1997, and some associations are sponsoring audit programs to verify this. CRN fully supports GMPs, and has taken an active role in creating and promoting the version currently under discussion. However, the IG's report may overestimate what can be accomplished merely by GMPs. The law already requires that products provide 100% of label claim, for example, and companies that flaunt that requirement are not likely to be brought into line merely because an additional regulation is in place supporting the requirement. The GMPs, in and of themselves, will not in fact be able to provide assurance of the precise contents of each batch manufactured. As is the case now with all other legal and regulatory requirements, any assurance provided will be the result of a combination of factors, including the companies' commitment to following GMPs and FDA's commitment to enforcing them.

Page 5, recommendation 4

The recommendation that FDA put more useful information on its website about adverse events may have value, provided it is made very clear what the limitations of adverse event reports are, particularly with regard to demonstrating any real association between a product and an event. It would be useful to consider limiting any publicly available adverse event information to some type of summary form, categorized by product types or generic ingredients. It should be noted that, in the food area, FDA has not published reports that identify adverse events by company or even product name, but rather has grouped events related to ingredients of potential concern (aspartame, sulfites, olestra). Similarly, reports prepared by the Poison Control Centers are summarized in broad categories and do not identify specific products or companies. This could provide a useful pattern for dietary supplement reports as well.

INTRODUCTION

Page 8, second line

This line says that reported events range in severity "from nausea and cardiac arrest to death." This is awkward phrasing. A suggested edit might incorporate two minor and

two major effects, such as: "Reported events range in severity from nausea or dizziness to cardiac effects or death."

Page 8, section on DSHEA

This is a good basic summary of DSHEA.

Page 8, section on "Our Inquiry"

The first sentence says "FDA's adverse event reporting system for dietary supplements is a particularly important safety valve for consumers due to the lack of other complementary oversight systems." This statement implies that dietary supplements are unique among FDA-regulated products in the lack of complementary oversight systems. This is not the case. Dietary supplements are a category of foods, and are no more lacking in oversight than are other foods, including conventional foods, functional foods, infant formula, and medical foods. It is entirely appropriate that the oversight systems should be the same for all these food categories.

This paragraph of the IG's report also falsely suggests that dietary supplements are not subject to manufacturer inspections. This is not the case. Dietary supplements are subject to manufacturer inspections, and the inspections that are conducted are often extensive, requiring several days to complete. These inspections are based on the same GMPs that apply to conventional foods, until such time as new dietary supplement GMPs are adopted.

This paragraph also suggests that the increased popularity of dietary supplements, by itself, is a risk factor for adverse events. This is not a logical statement. Foods, after all, are used by one and all, and their popularity or universal usage does not itself confer risk.

IMPORTANCE OF THE SYSTEM

Page 11, last paragraph

The IG's report says FDA has received only 38 new dietary ingredient notifications covering 32 ingredients. AAC Consulting has a commercially available database showing more than 100 new ingredient notifications, to date.

Page 12, chart on regulatory mechanisms

The box summarizing regulatory requirements should show that dietary supplements are subject to food GMPs until new dietary supplement GMPs are developed. Likewise infant formula is subject to food GMPs until new ones are developed.

Page 12, first paragraph under "popularity of dietary supplements"

This paragraph emphasizes: "Today, dietary supplements are widely available in grocery stores, retail pharmacies, health food stores, and on the Internet." Except for the internet aspect, this is not a new phenomenon, as the paragraph implies. Dietary supplements have been "widely available" in grocery stores, retail pharmacies, and health food stores for at least 60 years, if not longer.

Pages 13-14, warning labels on dietary supplements

The report notes that some dietary supplements bear warning statements about potential contraindications, even though FDA does not specifically require such warnings. The extensive efforts of industry associations to encourage appropriate warnings are dismissed with the statement, "Some industry groups have established standard warnings for certain products, but manufacturers' use of these standard warnings is voluntary." It would be more appropriate for the report to fully acknowledge the extent of the industry's efforts, especially with regard to controversial products such as ephedra. Although FDA has not yet finalized a regulation relating to ephedra, the industry has largely complied with trade association recommendations to include a very extensive warning statement on products containing ephedra. The warning is modeled on the OTC drug warning label for ephedrine-containing products. Some states have also passed laws requiring extensive warning statements for ephedra-containing products. Some associations have recommended warning statements for other products, and some have recommended dosage limits for ingredients that may present safety concerns. The associations which have been pro-active in this regard include the Council for Responsible Nutrition, the American Herbal Products Association, the Consumer Healthcare Products Association, the National Nutritional Foods Association, and the Utah Natural Products Alliance. These efforts deserve more attention and more credit than they are given in the present draft IG report.

This may also be an appropriate place to include some comment regarding the importance of consumer compliance with label directions. All dietary supplements recommend a specific level or range of use for the product, and many of the reported adverse event reports involve misuse or abuse of the product by the consumer.

Page 15, first paragraph

An FDA-commissioned paper by A. Walker is cited to the effect that adverse event reports capture only about 1 percent of actual adverse reactions. Is this paper available? CRN would appreciate the opportunity to review it.

Page 15, comparison to other adverse event reporting systems

The IG's report suggests that the large number of reports received by the Poison Control Centers provides a more realistic view of true consumer experience than the much

smaller number received by FDA. It should be noted, however, that all calls received by the Poison Control Centers are considered "reports," even if they involve no adverse event and possibly no ingestion at all. For example, if a mother finds her toddler on the floor with an open bottle of tablets and calls the Poison Control Center for advice, that is considered a report, even though the child may have no symptoms and may not in fact have even swallowed any of the tablets. It is also notable, and should be mentioned in this report, that the vast majority of reports received for dietary supplements by Poison Control Centers involve accidental exposures in young children rather than deliberate consumption by any age group, and result in no symptoms or minor symptoms. The report currently gives the incorrect impression that the thousands of reports received by the Poison Control Centers represent significant adverse events not captured by the FDA system, and this is not necessarily the case. If the State of Texas has received large numbers of reports, this is in part due to active solicitation of reports relating to ephedra-containing dietary supplements. CRN is aware that the state forwarded some of these reports to FDA, but is not aware of the reasons why all reports apparently were not forwarded. Perhaps only significant reports were forwarded.

Page 16, top of page

The first paragraph on this page says that manufacturers do not share adverse event information with FDA. The implication is that ONLY dietary supplements are exempt from mandatory reporting of adverse events. In fact, this is true of conventional foods as well as OTC drugs. Only prescription drugs or NDA drugs are required to report adverse events to FDA. The report should clarify these facts.

Page 16, paragraph on "presumed safety"

This paragraph states: "The presumed safety of dietary supplements may cloud the consumers' ability to link an adverse event with a supplement product." Is the implication that an attack should be mounted on "presumed safety"? The fact is that the vast majority of dietary supplements are safe when used as directed in labeling, or when used in the manner that is common among most consumers.

Page 16, paragraph on "self-care products"

This paragraph asserts that "another factor that may contribute to under-reporting of supplement adverse events is that they are self-care products." It should be acknowledged that many other products, including OTC drugs, are also self-care products. People also utilize conventional foods specifically for health purposes. It is a well established and valid assumption that people can and should take substantial responsibility for their own health care. This is a critical and positive aspect of overall health care in the U.S. By definition, "self-care" occurs mostly without the guidance of the physician. The IG's report inappropriately casts aspersions on the whole concept of self-care. This is in contrast to the findings of Congress at the time of the enactment of DSHEA, which recognized that better nutrition and supplementation can contribute to consumer health and can even help control escalating health care costs. DSHEA

emphasized that “consumers should be empowered to make choices about preventive health care programs based on data from scientific studies of health benefits related to particular dietary supplements.”

Page 19, first paragraph

The IG’s report indicates that FDA may need to test products to determine the actual ingredients and levels of each ingredient in the product. It would be appropriate to recognize at this point that there are in some cases a variety of methodologies available for analyzing some ingredients, and that there is a need for validated methods as well as good laboratory practices in order to ensure that appropriate results are obtained. Some of the publicity about variable levels of some ingredients has been based on inappropriate methods of analysis. The industry is currently supporting several efforts to establish validated analytical methods, including the INA/MVP program (Institute for Nutraceutical Advancement/Methods Validation Program), a new initiative being undertaken by AOAC, the ongoing efforts of the USP, and a new certification program recently launched by NSF.

Page 19, second paragraph

The IG’s report implies that the new dietary supplement GMPs will permit access to records not currently available for food products generally. It should be noted, however, that DSHEA does not include any specific change to the current law regarding access to records for foods generally, including dietary supplements.

Page 19, paragraph on “limited manufacturer information”

The IG’s report says nonreporting of adverse events by dietary supplement manufacturers “contrasts starkly” with the number of reports from pharmaceutical and device manufacturers, as if this were the correct comparison. In fact, the correct comparison is to reporting for OTC drugs and for foods, since these categories – like dietary supplements – are also self-care products and have no statutory requirement to report. It is hardly surprising that FDA receives numerous reports from those industries required by law to provide such reports.

Pages 19-20, characterization of the industry

The report paints a negative picture of the dietary supplement industry, implying that many companies are fly-by-night operations that FDA has difficulty locating. In fact, the vast majority of dietary supplements are manufactured by large corporations that are well known to the agency since they are regularly inspected. *Nutrition Business Journal* estimates that the largest 65 manufacturers in the business account for about 75% of the products on the market. The products these companies make are properly labeled, as required by regulations, but unfortunately product labels are not routinely submitted to FDA by individuals reporting an adverse event. The report indicates that FDA lacks a product label in 77% of the adverse event reports in the database, but fails to make the

point that the lack of a label may largely explain the agency's difficulty in identifying manufacturers and tracking products.

The IG's report incorrectly states that products sold through multi-level organizations may be especially difficult to track. CRN's membership includes many of the major multi-level marketers, and they indicate that their products bear the name and location of the company headquarters, not of a local distributor.

This is not to say that in all cases the company named on the label of a product will be the actual manufacturer of the product. Labeling regulations for all foods, including dietary supplements, require that the label show the name and address of the manufacturer, packer or distributor. This can become an issue when any company manufactures a food, drug, or dietary supplement which is marketed through another company. For example, major chains such as Safeway, CVS and Walmart typically sell their own store brands of many products, including dietary supplements, and these products are almost always manufactured by another firm. The chain may prefer that its name appear on the label as the distributor of the products, so that consumer complaints or inquiries will come to the chain rather than going to the actual manufacturer. In such cases, however, it is unlikely that FDA would face a major difficulty in obtaining the name of the actual manufacturer from the chain distributing the product.

Page 21, number of new ingredient notifications

The report says only 38 new ingredient notifications have been received, but AAC Consulting has a commercially available database indicating that more than 100 have been filed.

Page 21, section on consumer use

Once again, it is taken as a given that the correct comparison is between dietary supplements and prescription drugs. Dietary supplements are widely distributed and intended for self-selection, as are conventional foods and OTC drugs. The denominators of usage for dietary supplements, conventional foods, and OTC drugs are generally unknown, but large. Prescription drug practices are not the appropriate comparison.

Page 22, number of actions taken by FDA

CRN suggests that 31 safety actions from January 1994 to June 2000 is not a small number and does not support the IG's assertion that FDA "rarely" takes such actions. Also, the fact that FDA took only 31 actions during a period when more than 100 million people were taking dietary supplements is not necessarily low, let alone "strikingly low." During that period, it is likely that around 60 million of those people were specifically taking a multivitamin, and it is not at all surprising that not a single FDA action was taken against a multivitamin. In fact, it would be striking if any actions were taken against the multivitamin category, given the longstanding record of safe use of such products by a large fraction of the population.

The IG's report repeatedly presumes that the dietary supplement category is inherently risky and that the very prevalence of consumer use is a risk factor. This presumption is not justified, and the final report must be revised to more fairly reflect the actual safety profile of the most commonly used dietary supplement products. Over the decades, hundreds of millions of consumers have used dietary supplements on a regular basis. Many of those consumers are longterm satisfied users who have never experienced an adverse event associated with the dietary supplements that are an integral part of their efforts to construct a healthy lifestyle.

Pages 25-30: Recommendations

See CRN comments on the summary IG recommendations, in pages 2-5 of these comments.

APPENDIX A. FDA experience with ephedra-containing products

Page 31. ephedra discussion

The approved dosage of synthetic ephedrine for use in OTC drugs as a bronchodilator is incorrectly stated as "up to 25 mg a day." The correct statement would be that ephedrine is approved for use in OTC drugs as a bronchodilator at levels up to 25 mg per dose, with a maximum daily intake of up to 150 mg.

Pages 34-35. IG's commentary on criticisms of FDA's proposed rule on ephedra

These two pages cite some criticisms that have been raised regarding FDA's proposed rule on ephedra-containing products, and provide commentary from the IG's office. Curiously, in most cases the IG's commentary appears to CRN to be unrelated to the substance of the criticism cited. Examples are mentioned below.

Page 34. comment on meeting label claim

The IG's "commentary" in this section is unrelated to the criticism about FDA's selection of the 8 mg maximum dose. The criticism cited is that FDA's proposed limit of 8 mg is based in large part on the agency's analysis of the adverse event reports. The IG's commentary is related to the possibility that products may not always meet label claim, and therefore FDA needs product samples to permit analysis of the product actually used by consumers. These two points are not connected, since FDA did not select the 8 mg limit because of uncertainty about what products contain.

The IG's commentary implies that without GMPs there is no requirement for products to meet label claim. This is false. Under FDA regulations, all foods including dietary supplements are required to provide what the labels say they provide. Products that fail to do so are misbranded and illegal. In addition, DSHEA added a new provision

reiterating that dietary supplements are misbranded if they fail to have the identity and strength they are represented to have.

Page 34, commentary on FDA's reliance on adverse event reports rather than controlled research

The commentary relating to the new ingredient notification process is not relevant to ephedra, since ephedra is not a new ingredient. It was on the market well before the passage of DSHEA, and in fact some of the initial adverse event reports date from 1992. FDA had access to an abundance of clinical evidence on ephedrine alkaloids, which was discussed in depth at the 1995 and 1996 advisory committee meetings, but chose to rely primarily on some adverse event reports in its regulatory approach to ephedra.

Page 35, commentary on product usage associated with adverse events

The commentary relating to a pharmaceutical manufacturer's establishment of recommended usage levels is not relevant to the topic under discussion. The issue here is not the labeled directions, but the actual usage pattern of the individual for whom the adverse event was reported. People do not always use products – even prescription products – in the manner directed in labeling, and adverse event reports often do not provide information on the actual usage patterns associated with the adverse event.

Page 35, comment on denominator data

The importance of denominator data is overstated, especially since it has been noted elsewhere that a single well-documented report may be sufficient as a basis for action (as in the case of the plantain/digitalis problem).

APPENDIX B, pages 36-38

The list of 31 actions taken by FDA on safety of dietary supplements actually pertain to only a handful of products:

- Ephedrine alkaloids
- GHB, GBL and related products
- Digitalis/plantain mixup
- 5-hydroxy-L-tryptophan
- Triax metabolic accelerator
- Aristolochic acid

These represent a unique selection of products, most of which are not typical of dietary supplement ingredients. The vast majority of dietary supplements are notably absent from this list, since they by and large have an excellent safety record and do not generate any significant reason for concern. Almost half of total dietary supplement sales are accounted for by vitamins and minerals, which do not appear in this list. While CRN recognizes that there is some potential for toxicity from an excess of some vitamins and

minerals, actual reports of adverse events -- in the clinical literature or elsewhere -- are relatively rare. CRN has recommended voluntary dosage limitations for those nutrients such as vitamin A that are known to cause adverse effects when used in excess. Another quarter of the market is made up of a variety of botanical ingredients, most of which have an excellent safety record and most of which do not appear to any significant extent as the subject of adverse event reports. These include botanicals such as garlic, ginseng, and echinacea.

Products containing ephedrine alkaloids are probably the most physiologically active of the botanical products marketed in this country. Yet millions of consumers have used ephedra-containing products safely for weight loss and for sports nutrition, and have vigorously expressed their concern about state or Federal efforts that might restrict access to such products. Experts differ in their evaluation of the significance of the adverse events that have been reported in association with such products and in their recommendations regarding the regulatory actions that should be taken. Industry, FDA, and consumers will all benefit when there is a regulatory resolution to the longstanding issue of establishing appropriate parameters for the safe marketing of these products. In December 2000, CRN submitted to FDA an extensive evaluation of the safety of ephedra, prepared by toxicological experts at the firm of Cantox, and we are hopeful that this rigorous scientific evaluation will help FDA bring this issue to closure.

GHB and GBL are not legitimate dietary supplements, but are industrial chemicals or drugs masquerading as dietary supplements. GHB was on the market as a "designer drug" for years before DSHEA was passed, and is not a legitimate dietary supplement. GBL is an industrial chemical marketed as a floor stripper, and has been only temporarily using the dietary supplement category as a convenience. In fact, CRN understands that many purveyors of GBL have apparently now re-adopted the category of "floor stripper" in preference to the dietary supplement category. It is inappropriate to consider such products as in any way typical of the dietary supplement category.

The digitalis/plaintain issue was a clear case of a mixup, which happens with foods and even with prescription drugs from time to time. As soon as the mixup was identified, the product was the subject of an FDA warning and a recall. This was a good example of quick action based on an adverse event report, involving cooperation between FDA and the industry to promptly warn consumers and recall the product.

The triax problem evidently is a case of a company overtly adding a drug to a dietary supplement. CRN is not aware whether FDA action on this ingredient was triggered by an adverse event report.

The 5-hydroxy-tryptophan issue arose because of the purported similarity of a substance in this product to the contaminant responsible for the EMS outbreak related to L-tryptophan in the late 1980's, and was not triggered by the adverse event reporting system.

Aristolochic acid has long been recognized as a substance of concern, especially in Europe. FDA's current action was in reaction to European precedents and was not triggered by the adverse event reporting system.

The nature of the actions FDA has taken on the basis of safety concerns over the past six years, and the types of products involved in them, only serve to emphasize CRN's point that the overwhelming majority of dietary supplements are safe within a broad range of use, and the incidence of significant adverse events is limited to a relatively narrow spectrum of products. It is critical that discussion of the overall adverse event reporting system for dietary supplements be considered in this context.

**Comments of Sidney M. Wolfe, MD, Director
Public Citizen Health Research Group
on the HHS Inspector General's Study of
Adverse Event Reporting for Dietary Supplements**

We are very concerned about the dangerous inadequacy of FDA's adverse reaction reporting system for dietary supplements---wherein, for 1994 through 1999, the number of such reports filed with the American Association of Poison Control Centers (AAPCC) was 35,400, more than ten times higher than the approximately 3,000 reported to the FDA. This must be viewed, however, as just a symptom of the larger issue: the crippling effect that the Dietary Supplement Health and Education Act of 1994 (DSHEA) has had. However, it will not be possible to significantly remedy most of the health hazards which have arisen or will continue to arise as a result of that law without its repeal or, at the least, significant health-strengthening amendments. Despite this, the FDA has, in deference to the industry and its congressional supporters, refused to acknowledge the fact that their authority under the law has been so damaged. During a March 25, 1999 testimony before the House Government Reform Committee, Chairman Dan Burton asked FDA Commissioner Dr. Jane Henney, "Do you think that the FDA has enough authority right now to deal with dietary supplements?" Her answer was "I believe, as outlined in the act, appropriate authority is either given to the agency within the context of the Dietary Supplement Act or in the law that it is embodied in the basic FDA Act as well.We believe that we have the appropriate authorities that we need."

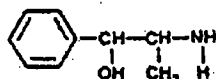
In recent testimony before the same committee, March 20, 2001, FDA Center for Food Safety and Applied Nutrition (CFSAN) director Joe Levitt reaffirmed Dr. Henney's official FDA policy against asking for more legislative authority and tried to make the case that as long as more financial resources were made available, CFSAN could do its job implementing DSHEA and would "provide consumers with a high level of confidence in the safety, composition and labeling of dietary supplements."

We agree with all of the limited Inspector General recommendations for additional legal authority and funding to improve FDA performance but the recommendations do not go far enough. Without the additional legal authority to require evidence of safety and effectiveness for dietary supplements as a condition of continued marketing, the FDA is still in the position of waiting until enough deaths or injuries have been caused by a specific dietary supplement and detected by the agency before pushing for a recall. In that context, the FDA relies on DSHEA authority to declare ingredients adulterated if they present "a significant or unreasonable risk of illness or injury." This after-the-fact form of regulation is painfully reminiscent of the situation for prescription drugs before 1938. In that earlier era FDA authority to take action against a drug could only occur after the agency bore the burden of showing, based on marketing

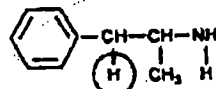
experience, that the drug's risks were unacceptable rather than the post-1938 requirement of placing the burden for establishing safety on the manufacturer.

The eagerness or guts to use even this limited present authority is questionable since the FDA has not yet acted to ban ephedra-containing products even though they clearly present "a significant or unreasonable risk of illness or injury." The following chart shows the close chemical structures of PPA, ephedrine and amphetamine:

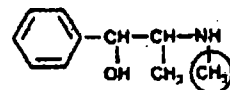
PHENYLPROPANOLAMINE



AMPHETAMINE



EPHEDRINE



It can be seen that the only structural difference between PPA, now banned because of its cardiovascular toxicity, and ephedrine is the existence of a CH₃ or methyl group on ephedrine instead of the H in the same position in PPA. The well-documented concerns about the cardiac (arrhythmias) toxicity and brain toxicity of ephedrine (also associated with a large number of strokes due to bleeding in the brain), the known brain toxicity of amphetamine and the use of amphetamine as an appetite suppressant confirm that there are pharmacological as well as chemical similarities between all of these compounds.

In addition to the excellent ephedra chronology included in the Inspector General's report there are two reviews of 140 adverse reaction cases reported by FDA consultants to the FDA involving the use of ephedra alkaloids that confirmed the cardiac toxicity of ephedra. The first study found that 47% of cases involved the cardiovascular system (17 cases of hypertension, 13 with palpitations or fast

heartbeat, 10 strokes). There were also 7 reports of seizures.¹ The second study found that of the 104 reports in which causation by ephedra was very likely, there were 10 cases of sudden death, nine cardiac arrhythmias, another 23 possible arrhythmic events, three heart attacks, ten cases of chest pain and 15 severe strokes.²

Short-term and Long-term Remedies

Right now, legislation should be introduced—combined with the right signals during the FDA appropriation process and a strong version of the Good Manufacturing Practice (GMP) regulations—to rapidly lessen the damage being done by this dietary supplement industry wish list having the force of, a federal law, DSHEA. These improvements include a mandatory adverse event reporting requirement for all dietary supplement manufacturers, mandatory warning labels for risks, requirements for company and product registration, and identification of the raw ingredients and the source (by country) for each of the ingredients in each product. This latter requirement is necessary to ensure that BSE-contaminated recycled cow organs do not appear on the shelves in this country as dietary supplements. In addition, mandated funds are necessary to implement and enforce the Good Manufacturing Practices regulation that will hopefully be finalized soon. In addition, the FDA should be appropriated the funds to purchase the entire dietary supplement database of the AAPCC. At present, only the ephedra alkaloid cases have been contracted for by the FDA.

In the long run, DSHEA will either be significantly modified or repealed so that pre-marketing safety and efficacy testing become the preferable alternative to post-marketing human experimentation.

¹ Haller CA, Benowitz NL. Adverse cardiovascular and central nervous system events associated with dietary supplements containing ephedra alkaloids. *New Engl J Med* 2000;343:1833-8.

² Letter from Ray Woosley, M.D., Ph.D, Georgetown University School of Medicine, August 18, 1999 to the FDA.



April 11, 2001

Mr. Michael F. Mangano
Acting Inspector General
Department of Health and Human Services
Room 5246 Cohen Building
330 Independence Avenue, S.W.
Washington, D.C. 20201

Dear Mr. Mangano:

The Center for Science in the Public Interest (CSPI)¹ submits these comments on the draft inspection report entitled, "Adverse Event Reporting for Dietary Supplements: An Inadequate Safety Valve."

I. We Support the Recommendations in the Draft Report

We fully concur with the view that the Food and Drug Administration's (FDA) adverse event reporting system for dietary supplements "is a particularly important safety valve for consumers due to the lack of other complementary oversight systems, such as premarket approval and manufacturer inspections, and the increased popularity of dietary supplements."²

We also agree with the report's recommendations that the FDA: (1) "facilitate greater detection of adverse events by requiring dietary supplement manufacturers to report adverse events to the FDA"; (2) "obtain more information on adverse event reports to generate stronger signals of public health concerns" and improve case follow-up by requiring supplement manufacturers to register and list their products with the FDA; (3) obtain clinical data from manufacturers and the National Institutes of Health and explore the possibility of a monograph system for dietary supplements that would contain safety and efficacy information on particular ingredients; and (4) "disclose more useful information to the public about dietary supplement adverse events on its website."

¹ CSPI is a non-profit consumer organization supported by 800,000 members that has worked since 1971 to improve national health policies.

² Office of Inspector General, *Adverse Event Reporting For Dietary Supplements An Inadequate Safety Valve* (Draft Report), Mar. 8, 2001 at 8 [hereinafter *Draft Report*].

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Executive Director
11-04

II. Increased Authority and Funding is Needed to Implement Effective Adverse Event Reporting System.

The existence of the problems discussed in the Draft Report has been known for a number of years, but pleas for increased funding to implement needed changes have not been heeded by Congress. During a May 27, 1999, appearance before the House Committee on Government Reform, Joe Levitt, Director of the Center for Food Safety and Applied Nutrition compared the mandatory adverse event warning system for drugs to the voluntary system in place for dietary supplements:

Compared to the CDER [Center for Drug Evaluation and Research] adverse event reporting system, the SN/AEMS [Special Nutritionals Adverse Event Monitoring System] lacks many of the tools at CDER's disposal -- premarket testing database, mandatory reporting by manufacturers, registration of firms and listing of products, good manufacturing practice requirements, and a mature internal database system with which to manage the wealth of information they receive.³

In comments on a July 2000 report by the General Accounting Office entitled, *Food Safety, Improvements Needed in Overseeing the Safety of Dietary Supplements and Functional Foods*, the FDA explained that:

... FDA continues to make progress toward accomplishing other related tasks for which funding is limited. For example, steps are underway to enhance FDA's adverse event reporting system, which includes reports regarding conventional foods and dietary supplements. As the draft [GAO] report notes, FDA continues to conduct an initial clinical review of all adverse event reports received. Furthermore, for all serious adverse events reported, FDA seeks additional information from consumers and health care providers to aid in proper assessment. *Because of resource constraints, FDA is able to perform risk assessments of only the most significant public health issues associated with the use of the products. To date, the only dietary supplement public health issue for which an extensive risk assessment has been performed is for ephedrine alkaloids.* These adverse events account for around 40% of the adverse events received. FDA has, however, conducted Health Hazard Evaluations on a number of other dietary supplements such as chapparel, lead contaminated bee products, selenium overdosage, and digitalis-contaminated plantain.⁴

³ Statement by Joseph A. Levitt, Director Center for Food Safety and Applied Nutrition, FDA before the Committee on Government Reform, U.S. House of Representatives, May 27, 1999 at 7, <<http://www.verity.fda.gov>>.

⁴ U.S. General Accounting Office, *Food Safety, Improvements Needed in Overseeing the Safety of Dietary Supplements and "Functional Foods,"* GAO/RCED-00-156 (July 2000) at 38

At a more recent hearing, Joe Levitt told the same committee that dietary supplements are allocated only \$6-million out of the \$1-billion budget for FDA. Levitt stated that "it's virtually our smallest program."⁵

At a minimum, the FDA needs specific statutory authority and sufficient funding to establish a mandatory registration and listing system for manufacturers and dietary supplements. As detailed in the Draft Report, FDA sorely needs a list of supplement products and their ingredients as a quick, easy reference when it receives an adverse event report. Moreover, the FDA needs to be able to contact manufacturers promptly and notify them when it has received an adverse event report. And, it needs the software necessary to analyze any data it receives on adverse effects.

Congress has previously authorized registration and product listing requirements for drugs, medical devices and infant formula. Recent safety concerns indicate that it is now essential that Congress grant FDA the statutory authority to impose registration and listing requirements for supplements and provide the agency with funding sufficient to implement such requirements.

III. The FDA Should Support a Systematic Study of Dietary Supplements

Although thousands of dietary supplement products are on the market, most supplements in use have not been tested for safety and efficacy in well-controlled clinical trials. In addition, manufacturers sell traditional herbal medicines for non-traditional purposes. An 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. For example, some traditional Chinese herbs for respiratory ailments are sold in the U.S. for non-traditional purposes such as dieting or body building. 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 others based on dose, duration of use, preexisting conditions and other factors.

Also, many consumers do not understand that if a supplement such as an 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.

Problems related to the safety of dietary supplements have been widely reported in the

(emphasis added).

⁵ *US says lack of funding hampers supplement law*, Reuters, Mar. 21, 2001.

media and many consumers are becoming concerned. Such problems, coupled with increasing skepticism about exaggerated claims, may be having an impact on the industry; recent sales figures indicate that supplement sales seem to have reached a plateau. By continuing to oppose greater regulation, the dietary supplement industry may be harming its own long term interests.

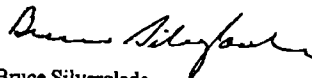
It is, therefore, in the interest of both industry and consumers, to support a systematic, comprehensive review of dietary supplement safety and efficacy. (Vitamin and minerals known to be Generally Recognized as Safe (GRAS), and whose role in maintaining health is not the subject of controversy within the scientific community, could be exempted from the review). The results of such a study would provide greater legitimacy for dietary supplements that are truly beneficial and could lead to the removal from the marketplace of any dangerous products that could injure consumers and tarnish the reputation of the entire industry.

The U.S. National Academy of Sciences (NAS) is beginning an FDA-funded project to develop seven prototype monographs on leading dietary supplement ingredients. That is a start. Congress should provide additional funds for this project so that it can be expanded to cover all of the most popular dietary supplements now on the market. Ultimately, regulatory agencies must be empowered to act swiftly on any recommendations of the NAS, so as to protect consumers and maintain the credibility of the industry as a whole.

Dietary-supplement consumers deserve no less. 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.

Thank you for letting us review this important new report.

Sincerely,



Bruce Silverglade
Director of Legal Affairs



Ilene Ringel Heller
Senior Staff Attorney

Endnotes

1. 21 U.S.C. sec. 321 (1994).
2. T. E. McAlindon, et al., "Glucosamine and Chondroitin for Treatment of Osteoarthritis," *Journal of the American Medical Association* 238 (March 15, 2000) 111: 1469-1475.
3. T. J. Wilt, et al., "Saw Palmetto Extracts for Treatment of Benign Prostatic Hyperplasia," *Journal of the American Medical Association* 280 (November 11, 1998) 18: 1604-1609.
4. 21 C.F.R. sec.101.79.
5. *How Accurate is the FDA's Monitoring of Supplements Like Ephedra?: Before the House Comm. on Government Reform*, 106th Cong., 1st Sess. (1999) (statement of Joseph A. Levitt, Director, Center for Food Safety and Applied Nutrition, Food and Drug Administration).
6. Dietary Supplement Health and Education Act of 1994, Pub. L. No. 103.417 sec. 2.
7. 21 U.S.C. sec. 342 (1994).
8. It is important to note that the Federal Trade Commission also has jurisdiction over dietary supplements. It regulates any type of advertising of dietary supplements on television, in print, or on the Internet, to ensure that false claims are not made.
9. "High concern list of products/ingredients: The criteria for inclusion on this list will minimally include: 1) Targeted high frequency occurrences from the database or 2) information from other sources (scientific literature or that submitted to FDA by interested parties [consumers, scientists, industry, etc.]) citing deaths or aggregate system failure, and from information of other sources.

Serious event: For the purpose of evaluation, a medically serious adverse event implies a diagnosis or condition that is dangerous, critical, or alarming. At a minimum, a medically serious adverse event would include all the definitions under Medwatch. (Medwatch definition of serious: When the outcome is death, life threatening (real risk of dying), hospitalization (initial or prolonged), disability (significant, persistent, or permanent), congenital anomaly, or required intervention to prevent permanent impairment or damage.) Other medical events that may not be immediately life-threatening, but which require intervention to prevent one of the Medwatch definitions would be considered medically serious.

Clinically significant: an event, when occurring in healthy general populations, requires minimal intervention or supportive care, but when occurring in vulnerable populations (infant, children, immunocompromised, elderly, or otherwise debilitated individuals), often results in increased morbidity and/or prominent sequelae." FDA, *Standard Operating Procedures*, November 28,

1999.

10. 21 U.S.C. sec. 402(f)(1)(A) (1994) contains the standards for which a dietary supplement is adulterated. The standards for adulterated food also apply to supplements in sec. 402 (a-e and g).

11. 21 U.S.C. sec. 350 b (1994).

12. 21 U.S.C. sec. 402(f)(1)(B) (1994).

13. P. Kurtzweil, "An FDA Guide to Dietary Supplements," *FDA Consumer* (1999): Publication No. (FDA) 99-2323.

14. "Annual Industry Overview 2000," *Nutrition Business Journal* 5 (2000) 7/8.

15. U.S. Food and Drug Administration Center for Food Safety and Applied Nutrition, *Economic Characterization of the Dietary Supplement Industry Final Report*, March 1999.
[<http://vm.cfsan.fda.gov/~comm/ds-econt.html>]

16. *Consumer Use of Dietary Supplements*, Prevention Magazine, 2000, 19.

17. *Ibid.*, 15.

18. *Ibid.*, 37.

19. A survey of 43,000 households found that the largest percentage of households (30 percent) with a member who used a supplement in the past 6 months was 60 years or older. P. Wingate, "Consumers Not Supplement Brand Savvy," *Natural Food Merchandiser*, March 1998.

20. *Dietary Supplement Health and Education Act: Is the FDA Trying to Change the Intent of Congress?: Hearing Before the House Comm. On Government Reform*, 106th Congr., 1st Sess. (1999) (statement of Jane E. Henney, Commissioner, Food and Drug Administration).

21. *Consumer Use of Dietary Supplements*, Prevention Magazine, 2000, 74.

22. K. J. Rothman et al., "Teratogenicity of High Vitamin A Intake," *New England Journal of Medicine* 333 (1995) 21: 1369-1373.

23. M. Rosenblatt et al., "Spontaneous Hyphema Associated with Ingestion of Ginkgo Biloba Extract [Letter]," *New England Journal of Medicine* 336 (1997) 15: 1108.

24. *Consumer Use of Dietary Supplements*, Prevention Magazine, 2000, 37 and 39.

25. S. C. Piscitelli et al., "Indinavir Concentrations and St John's Wort [Letter]," *Lancet* 355 (February 12, 2000) 9203: 547-548.

26. N. R. Slifman, et al., "Contamination of Botanical Dietary Supplements by *Digitalis Lanata*," *New England Journal of Medicine* 339 (September 17, 1998) 12: 806-811.
27. R. J. Ko, "Adulterants in Asian Patent Medicines [Editorial]," *New England Journal of Medicine*, 339 (September 17, 1998) 12: 847.
28. California Department of Health Services, "State Health Director Warns Consumers About Prescription Drugs in Herbal Products," Press Release No. 09-00, February 15, 2000.
29. G. Gugliotta, "Diet Supplement Maker Given Jail Time," *Washington Post*, Saturday, 8 July, 2000, section A5.
30. Other common names we found for ephedrine alkaloids include: Aradian tea, Khat, Miraa, Katstrauch, te de Arabia, Broomweed, Teaplant, arrow-leaf sida, Cuban-jute, Paddy's-Lucerne, Queensland-Hemp, Kubajute, Cha-Bravo, Escoba, Common Yew, Eibe, Ban-Xia, European Aconite, and Monk'Shood.
31. 21 C.F.R. sec. 104(h).
32. American Herbal Products Association, *Herbs of Commerce* (1992), 26.
33. A. Walker, "The Relation between Voluntary Notification and Material Risk in Dietary Supplement Safety," *FDA Commissioned Paper*, March 9, 2000.
34. *Consumer Use of Dietary Supplements*, Prevention Magazine, 2000, 74.
35. American Association of Poison Control Centers, *1999 Annual Report of the American Association of Poison Control Centers Toxic Exposure Surveillance System*, 1999.
36. It is important to note that Poison Control Centers use a broader definition for adverse event reports than FDA so the 13,000 may be somewhat high. For example, these reports may contain accidental ingestion by a toddler.
37. The Texas reports may also contain reports from Texas' Poison Control Center.
38. Lawsuit of Texas vs. Alliance, Texas Docket #3:94CV1002J; "FDA Stops Tracking Herbal Remedies: Agency Says it Doesn't Have the Funding to Assess Adverse Reactions," *San Francisco Chronicle*, Monday, 14 February, 2000.
39. Dietary Supplement Health and Education Act of 1994, Pub. L. No. 103.417 sec. 2.
40. A recent survey found that nearly half of consumers who were taking supplements to treat or prevent a common illness took herbal products instead of over-the-counter medications. *Consumer Use of Dietary Supplements*, Prevention Magazine, 2000, 39.

41. R. Davis, "Patients Fail to Fess Up on Herbal Remedies," *USA Today*, 29 May, 2000.
42. *Consumer Use of Dietary Supplements*, Prevention Magazine, 2000, 71.
43. By FDA's database we mean the database that FDA uses internally for its operations. We are not referring to the information that is publicly available on adverse event reports on the Internet.
44. In a random sample of adverse event reports associated with dietary supplements containing ephedrine alkaloids (92 out of 864 reports), GAO found that 62 percent of the sampled reports did not include medical records. U.S. General Accounting Office, *Dietary Supplements: Uncertainties in Analyses Underlying FDA's Proposed Rule on Ephedrine Alkaloids*, GAO/HEHS/GGD-99-90, July 1999, 11.
45. The remaining 32 percent of reports came from various sources including Poison Control Centers, State health departments, and family members.
46. A. S. Mitchell et al., "Patients as a Direct Source of Information on Adverse Drug Reactions," *British Medical Journal* 297 (Oct 8, 1988) 6653: 891-893.
47. 21 C.F.R., sec 101.36 (c).
48. A report conducted by ConsumerLab.com in January 2000 found that out of 13 brands of SAM-e, a dietary supplement used to treat depression, that it tested only 7 contained the amount listed on the label. ConsumerLab.com, "Product Review: SAM-e," 2000. [<http://consumerlab.com/results/same.html>]
- Another report conducted by ConsumerLab.com in January 2000 found that of 25 brands of glucosamine, chondroitin, and the combination of the two, 6 products did not have the amount of chondroitin listed on the label. ConsumerLab.Com, "Product Review: Glucosamine and Chondroitin," 2000. [<http://consumerlab.com/results/gluco.html>]
49. B. J. Gurley et al., "Content Versus Label Claims in Ephedra-Containing Dietary Supplements," *American Journal of Health Systems Pharmacists* (May 15, 2000) 57: 963-951.
50. Interestingly, The Dietary Supplement Health Education Act (DSHEA) stated that the good manufacturing practices (GMPs) regulations should be modeled after those in place for food products. However, if this is true, some are concerned that necessary tests would be excluded from the GMP regulations. For example, tests of active ingredient concentrations are not relevant for food products. It is also important to note that FDA may be able to inspect firms currently under the food good manufacturing practices.
51. Manufacturers of drugs under new drug applications must report all adverse events they receive to FDA. 21 C.F.R., sec. 314.80 (c) and 21 C.F.R., sec. 600.80 (c).

52. 21 C.F.R., sec. 101.5.

53. About 20 percent of supplement companies are multi-level. “Annual Industry Overview 2000,” *Nutrition Business Journal*, 5 (2000) 7/8.

54. FDA has requested that interested parties submit any clinical data that they may have on the safety of specific ingredients that it has identified as a potential concern, such as ephedra.

55. FDA does have the authority to take other enforcement actions such as criminal prosecutions but for the purposes of this report we did not examine these types of actions.

56. There is a disclaimer on the website that “there is no certainty that a reported event can be attributed to a particular product or ingredient.”

57. FDA added a link to its Corrections Page explaining that the product was not produced by the listed manufacturer. However, a search of the website by manufacturer does not include that reference to the Corrections Page.

58. The President’s Budget for Fiscal Year 2000 and Fiscal Year 2001 requested \$2.5 million for FDA’s adverse event reporting system for dietary supplements and both times it was rejected.

59. *Committee Report House Report 106-619*, Agriculture, Rural Development, Food and Drug Administration, and Related Agencies Appropriations Bill, 2001, “The Committee instructs the Food and Drug Administration to report to the Committee, within 6 months of enactment of the bill, on the dollar cost to implement the Dietary Supplement Strategy 10 Year Plan. The Committee instructs the Food and Drug Administration to report to the Committee within 6 months of enactment of the bill, a summary of the total dollar amount spent in fiscal year 2000 in assessing the safety of dietary supplements, and in meeting the legal statutory burden under the Dietary Supplement Health and Education Act of 1994 for demonstrating safety problems with dietary supplements.”

60. “Unfortunately, the realities in our industry today require that we focus on core problems and challenges not successes, agree on remedial tasks and swiftly implement Council for Responsible Nutrition’s problem solving action plan, not bask in the light of earlier achievements. The core challenges to the dietary supplement industry rest upon the declining confidence in dietary supplements by consumer, health care professionals, policymakers, and the media, which feeds the information flow of concern.” Council for Responsible Nutrition (CRN), “Agenda for Action: Strengthening Confidence in Dietary Supplements, State of the Industry Presentation,” CRN 2000 Annual Conference, Miami, FL, September 18, 2000, 4.

“Now the potential exists for negative backlash. There is scant evidence to prove this for 1999, but consumer disappointment, the relative lack of science and several other factors are undermining demand in herbs...” “Annual Industry Overview 2000,” *Nutrition Business Journal*.

5 (2000) 7/8, 3.

61. U.S. General Accounting Office, *Food Safety: Improvements Needed in Oversight of Dietary Supplements and "Functional Foods,"* GAO/RCED-00-156, July 2000.; *Report Of The Commission On Dietary Supplement Labels*, Commission on Dietary Supplement Labels, November 1997.

62. Some pharmacies provide optional forms for customers to list all of the medications they are taking, including dietary supplements. With this information, pharmacists would be particularly well-poised to detect drug-supplement interactions.

63. "Examination of the Evolving Science for Dietary Supplements," contract between FDA and National Academy of Sciences, effective September 30, 2000, section C, 4.

64. As of September 2000, United States Pharmacopeia (USP) had finalized one or more sets of standards for eleven dietary supplement ingredients. "Status of USP-NF and USP-DI Botanical Monograph Development." [<http://www.usp.org>]

65. Standardization of botanicals has three components: standardizing the part of the plant from which the extract derives, assuring that the botanical extract contains the amount listed on the label, and ensuring that the botanical is not adulterated by pesticides, heavy metals, or other contaminants. Because "acceptance criteria," such as benefits, safety, or nutritional value, have not been established for dietary supplements, USP must base its content standards on "ranges observed in currently marketed supplements deemed to be safe." United States Pharmacopoeia, *Draft Proposal: USP Quality Demonstration Program for Dietary Supplements*, August 2000. [<http://www.usp.org>].

66. United States Pharmacopoeia, *Draft Proposal: USP Quality Demonstration Program for Dietary Supplements*, August 2000, 4-5. [<http://www.usp.org>]

67. M. Blumenthal et al., "FDA Hearing Portends Uncertain Future for Mahuang: Members of FDA Panel Divided on Fate of Controversial Herb," *HerbalGram* (1996) 38: 29.

68. Food and Drug Administration Center for Food Safety and Applied Nutrition, Docket # OON-1200, *Assessment of Public Health Risks Associated with the Use of Ephedrine Alkaloid-containing Dietary Supplements* (March 31, 2000), 11.

69. As of July, 2000, seven States had enacted laws restricting the sale of dietary supplements containing ephedrine alkaloids in some way: Florida, Michigan, Nebraska, New York, Ohio, Texas, and Virginia.

70. The American Herbal Products Association (AHPA), a dietary supplement trade group, established guidance for the responsible sale of products containing ephedrine alkaloids in 1994.

After several iterations, its current guidelines recommend serving limits of 25 mg; require labels to state the amount of ephedrine alkaloids in the product; require labels to caution against use by those under 18, those with certain pre-existing conditions, and use in excess of recommended dosages; and prohibit marketing of these supplements as “street drug alternatives.” These guidelines are currently supported by other key dietary supplement trade groups. Adherence to these guidelines is strictly voluntary and many manufacturers of these supplements do not belong to the trade groups supporting these guidelines. AHPA, “Statement of Michael McGuffin President AHPA before the DHHS,” Public meeting on the safety of dietary supplements containing ephedrine alkaloids, August 8, 2000. [<http://www.ahpa.org/ephedrafda8800.html>]

71. Food and Drug Administration, Center for Food Safety and Applied Nutrition, “Illnesses and Injuries Associated with the Use of Selected Dietary Supplements,” 1993. [<http://vm.cfsan.fda.gov/~dms/ds-ill.htm>]

72. U. S. Department of Health and Human Services, “FDA Warns Consumers Against Nature’s Nutrition Formula One,” *HHS News*, February 28, 1995. [<http://vm.cfsan.fda.gov/~lrd/form1.html>]

73. Food and Drug Administration, Center for Food Safety and Applied Nutrition, Docket # OON-1200, *Assessment of Public Health Risks Associated with the Use of Ephedrine Alkaloid-containing Dietary Supplements*, (March 31, 2000), 2. Also, “Minutes of the Special Working Group on Food Products Containing Ephedrine Alkaloids of the FDA Food Advisory Committee,” October 11-12, 1995.

74. U. S. Department of Health and Human Services, “FDA Statement on Street Drugs Containing Botanical Ephedrine,” *HHS News*, April 10, 1996. [<http://vm.cfsan.fda.gov/~lrd/hhsephe1.html>]

75. Food and Drug Administration Center for Food Safety and Applied Nutrition, Docket # OON-1200, *Assessment of Public Health Risks Associated with the Use of Ephedrine Alkaloid-containing Dietary Supplements*, (March 31, 2000), 3. Also, Minutes of the FDA Food Advisory Committee Meeting on Dietary Supplements Containing Ephedrine Alkaloids, August 27-28, 1996.

76. 62 Fed. Reg. 30677-30724, June 4, 1997 “Dietary Supplements Containing Ephedrine Alkaloids: Proposed Rule.”

77. FDA Warns Against Drug Promotion of “Herbal Fen-Phen,” *FDA Talk Paper*, November 6, 1999. [<http://vm.cfsan.fda.gov/~lrd/tpfenphn.html>]

78. General Accounting Office, *Dietary Supplements: Uncertainties in Analyses Underlying FDA’s Proposed Rule on Ephedrine Alkaloids*, GAO/HEHS/GGD-99-90, July 1999.

79. *Ibid.*, 23.

80. 64 Fed. Reg. 17474-17477, April, 3, 2000 “Dietary Supplements Containing Ephedrine Alkaloids; Withdrawal in Part.”

81. FDA, “‘Dear Colleague’ letter about August 8, 2000 public meeting concerning the safety of dietary supplements containing ephedrine alkaloids,” June 8, 2000. [<http://vm.cfsan.fda.gov/~dms/ds-ltr6.html>]

82. From transcript of U. S. Department of Health and Human Services, Office of Women’s Health’s Public Meeting on the Safety of Dietary Supplements Containing Ephedrine Alkaloids, (August 8, 2000), 5-6.

83. For example, a controlled clinical trial on the safety and effectiveness of ephedrine alkaloids, conducted by Harvard Medical School and Columbia Presbyterian Hospital, was designed in 1996. As of September, 2000, results of this study were still not available.

84. General Accounting Office, *Dietary Supplements: Uncertainties in Analyses Underlying FDA’s Proposed Rule on Ephedrine Alkaloids*, GAO/HEHS/GGD-99-90, July 1999, 11.