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DIETARY SUPPLEMENTS FOR WEIGHT LOSS

Limited Federal Oversight Has Focused More on Marketing than on Safety

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Mr. Chairman and Members of the Subcommittee:

I am pleased to have the opportunity to testify as the Subcommittee considers concerns about dietary supplements that are used for weight loss.[1] Since the enactment of the Dietary Supplement Health and Education Act (DSHEA) in 1994, U.S. sales of weight loss supplements have increased steadily. The sales revenue of weight loss supplements—reported to be the fastest growing segment of the dietary supplement industry—increased 10 to 20 percent annually from 1997 to 2001, and industry officials expect that rate of increase to continue. The prevalence of obesity has increased in the United States, and many Americans are looking for ways to help them lose weight. It is estimated that Americans spent almost $2 billion on weight loss supplements in 2001. As sales of weight loss supplements have increased, so have concerns associated with their marketing and use. Regulators, medical experts, and the dietary supplement industry recognize that some weight loss supplements may be marketed with overstated claims, such as "lose weight while you sleep." In addition, some weight loss supplements have been reported to be associated with serious side effects for some people.

Various government agencies have a responsibility for oversight, research, and education efforts related to weight loss supplements. The Federal Trade Commission (FTC) and the Department of Health and Human Services' (HHS) Food and Drug Administration (FDA) have oversight responsibility for products marketed as weight loss supplements. Marketing includes both advertising activities and product labeling. FDA oversees the manufacture and labeling of weight loss supplements, but is not required by DSHEA to approve dietary supplements for safety or efficacy. FTC is responsible for ensuring that the advertising for these products is not unfair or deceptive. HHS's National Institutes of Health (NIH) funds research to determine the safety and efficacy[2] of weight loss supplements. All three agencies carry out some consumer education activities. State agencies also enforce individual states' laws that govern the sales and marketing of particular supplements.

[1]Generally, when we refer to weight loss supplements, we are referring to individual ingredients, not specific products or brands, some of which might contain multiple ingredients. Weight loss supplements include herbal or other botanical ingredients such as aloe, ephedra, fiber, and green tea; minerals such as chromium and pyruvate; as well as amino acids, enzymes, and tissues from organs or glands.

[2]Efficacy is the ability of a substance to produce the intended effect under ideal conditions of use.

Because of the concerns surrounding the marketing and use of weight loss supplements, you asked us to examine these issues and how they are being addressed by federal and state agencies and the dietary supplement industry, as well as in the courts. My remarks today will focus on (1) safety and efficacy concerns associated with weight loss supplements; (2) federal oversight, research, and public education efforts; and (3) state and local regulatory efforts aimed at consumer protection, including litigation concerning weight loss supplements.

In our examination of these issues, we reviewed scientific literature about weight loss supplements, as well as federal and state regulatory activities involving weight loss supplements. In addition, we interviewed and obtained documents from officials at FDA, FTC, and NIH. We also interviewed representatives of trade associations and interest groups pertinent to dietary supplements and weight loss. We identified dietary supplements commonly used or marketed for weight loss and possible side effects or contraindications for those supplements (see the appendix for a list of these supplements).[3] However, our work does not represent an exhaustive review of the efficacy or safety of particular weight loss supplements, nor did we look at meal replacements, over-the-counter drugs, or prescription medications. We provided a draft of this testimony to FTC, FDA, and NIH for their review. In oral comments, the Director of FDA's Center for Food Safety and Applied Nutrition agreed with our statement. FTC and NIH declined to provide official comments. FTC, FDA, and NIH provided technical comments which we have incorporated where appropriate. We conducted our work from May through July 2002 in accordance with generally accepted government auditing standards.

In summary, little is known about whether weight loss supplements are effective, but some supplements have been associated with the potential for physical harm. Health consequences, which can be serious, may result from the use of the supplement itself or from the interaction of the supplement with medications or foods. People with certain underlying health conditions, such as heart disease, high blood pressure, and diabetes, may be particularly at risk. In addition, supplements may be contaminated with harmful ingredients or may not contain the amount of an active ingredient that is stated on the label. Federal and state activities

[3]Although we did not focus on supplements that are marketed exclusively as performance enhancement supplements, some supplements with weight loss claims also make performance enhancement claims.

related to weight loss supplements have been limited and have focused on oversight of marketing more than on oversight of safety. FTC has prosecuted manufacturers of weight loss supplements for making misleading claims. FDA has issued warnings for some products and ingredients. However, FDA faces difficulty in addressing safety concerns due in part to weaknesses in its adverse event reporting system. The agency must also meet different standards for addressing safety concerns with supplements than it uses for drugs. Further, FDA has been slow to issue good manufacturing practice (GMP) regulations. Federal agencies have also been involved in research and education. NIH's National Center on Complementary and Alternative Medicine (NCCAM) has determined that weight loss supplements are not as high a priority as its other areas of research. Both FTC and FDA have developed publications and Internet sites on weight loss that provide some educational materials to consumers. In addition, several states have statutes or regulations in effect or pending to restrict the sale of some weight loss supplements. Some state attorneys general and local district attorneys have sued the manufacturers of supplements marketed with weight loss claims, and individuals have sued over injuries.

Background

More than half of U.S. adults are overweight or obese, and more than one-third of U.S. adults are trying to lose weight.[4] Increasingly, they are turning to weight loss supplements for help. The most widely used weight loss supplement is ephedra, or *ma huang*. The active ingredients in ephedra—ephedrine alkaloids—are compounds with potentially powerful stimulant effects on the nervous and cardiovascular systems. The dietary supplement industry estimates that as many as 3 billion servings of ephedra are sold each year in the United States and approximately 12 million individuals were using ephedra in 1999.

FDA regulates dietary supplements under DSHEA, which covers vitamins, minerals, herbs or other botanicals, amino acids, certain dietary substances, or derivatives of these items. A product that contains any active ingredient not on the preceding list—such as synthetic ingredients that are sold in over-the-counter drugs and prescription medications—may not be marketed as a dietary supplement. DSHEA requires that dietary supplement labels include complete lists of ingredients and the amount of

[4]A.H. Mokdad and others, "The Continuing Epidemics of Obesity and Diabetes in the United States," *Journal of the American Medical Association*, vol. 286 (2001), pp. 1195-1200.

each ingredient in the product. Products may be labeled as "proprietary blends" and must list all ingredients but do not need to list the amount of each ingredient. In addition, dietary supplements cannot be promoted as a treatment, prevention, or cure for a specific disease or condition. To the extent that therapeutic claims are made, FDA may take action.

FDA generally oversees the safety of dietary supplements. It may issue a regulation, for example, to prevent the further marketing of dietary supplements that it has determined pose an unreasonable risk of illness under the recommended conditions of use. A dietary supplement may also be removed from the market if HHS finds that it poses an imminent hazard to public health and safety. However, under DSHEA, it is the manufacturer who is responsible for ensuring the safety of the weight loss supplements it sells. Dietary supplements do not need approval from FDA before they are marketed. DSHEA does not require manufacturers to register with FDA,[5] identify the products they manufacture, or provide reports of adverse events—harmful effects or illnesses—to FDA. However, FDA is authorized to issue regulations governing GMPs to standardize manufacturing, packaging, and holding practices.

Since manufacturers of dietary supplements are not required to provide reports of adverse events to FDA, the agency and others rely on voluntary postmarketing reporting of adverse events to better understand the safety of dietary supplements. In addition to these adverse event reports, FDA uses data from poison control centers, reports and inquiries from consumers and health care providers, and complaints from trade competitors to track potentially dangerous supplements. These reporting systems can then be used to signal safety concerns. There are numerous problems with this passive system of adverse event reporting, and these have been noted extensively in our earlier work.[6] For example, only a small proportion of adverse events are reported, and those reports often are incomplete or contain inconsistent information.

[5]Under the Public Health Security and Bioterrorism Preparedness and Response Act of 2002, Publ. L. No. 107-188, manufacturers and distributors of dietary supplements will now be required to register with FDA no later than Dec. 13, 2003.

[6]U.S. General Accounting Office, *Dietary Supplements: Uncertainties in Analyses Underlying FDA's Proposed Rule on Ephedrine Alkaloids*, GAO/HEHS/GGD-99-90 (Washington, D.C.: July 2, 1999), and *Health Products for Seniors: "Anti-Aging" Products Pose Potential for Physical and Economic Harm*, GAO-01-1129 (Washington, D.C.: Sept. 7, 2001).

In an effort to control unfair or deceptive acts or practices in the marketplace, FTC oversees dietary supplement advertising to ensure that product claims are truthful and substantiated. Manufacturers and distributors of weight loss supplements make a wide variety of claims about how their products work. They claim that the supplements reduce appetite or cravings, increase metabolic rate, have a laxative effect, and block digestion of fat, carbohydrates, sugars, or starches. Manufacturers frequently combine multiple supplements into single products, promoting several pathways to weight loss. FTC can demand that false, exaggerated, or unsubstantiated claims be removed from advertising, and it also can seek monetary relief for injurious conduct. The marketing of unsafe products or potentially dangerous products without adequate safety warnings could violate the Federal Trade Commission Act.

Federal research regarding the safety and efficacy of weight loss supplements marketed to the public is carried out under NIH sponsorship. The agency's NCCAM is primarily responsible for federal research on complementary and alternative medicine, including dietary supplements, although other NIH institutes may also fund such research. Generally, NCCAM funds clinical trials to evaluate the safety and efficacy of popular alternative medicine products and therapies of interest. NIH's Office of Dietary Supplements (ODS) supports research and disseminates research results in the area of dietary supplements. Specifically, ODS plans, organizes, and supports conferences, workshops, and symposia. Although ODS can initiate such activities, it generally works in conjunction with other NIH institutes and centers and other groups.

States and individuals can also take action against manufacturers of weight loss supplements. States can enact and enforce laws and regulations to protect consumers from dangerous weight loss supplements and false or misleading advertising. Individuals can file lawsuits against manufacturers alleging injury from using weight loss supplements.

Little Evidence of Efficacy Exists for Weight Loss Supplements, and Some May Have Serious Health Consequences for Certain Individuals

There is little evidence on whether weight loss supplements are efficacious. However, we identified several ways that weight loss supplements might cause health risks. Many weight loss supplements have been associated with side effects, some of which can be serious. Some weight loss supplements should be avoided by individuals with certain medical conditions because particular effects of the supplements could exacerbate the conditions. In addition, some weight loss supplements have potentially dangerous interactions with prescription or over-the-counter medications or foods. Further, a supplement may contain dangerous contaminants or different amounts of an active ingredient than indicated on the product label. Finally, we found multiple-ingredient products to be of particular concern because of the increased difficulty involved in evaluating and understanding their safety.

Little Evidence Exists on Efficacy of Weight Loss Supplements

For most weight loss supplements, little scientific evidence to date supports their efficacy. Although there have been studies on specific ingredients, many of these studies have been of short duration, involved small numbers of individuals, or used study approaches that limited the usefulness of their findings. There have been few comprehensive reviews or long-term studies of efficacy. One comprehensive review of alternative treatments for weight loss found no reliable scientific evidence for the efficacy of any of the weight loss supplements that it reviewed.[7] Another review found similar results except for ephedra.[8] Most of the research that has been done to evaluate the efficacy of weight loss supplements has involved ephedra. A recently published randomized study found that a combination of ephedra and kola nut (a source of caffeine) promoted

[7]G. Eggar and others, "The Effectiveness of Popular, Non-prescription Weight Loss Supplements," *Medical Journal of Australia*, vol. 171 (1999), pp. 604-8. This study examined bladderwrack (*Fucus vesiculosus)*, brindle berry (*Garcinia cambogia*), caffeine/guarna, capsaicin, chitosan, chromium picolinate, ginkgo biloba, grapeseed extract, horse chestnut (escin), L-carnitine, lecithin, pectin, St. John's wort, and sweet clover/soybeans (isoflavones).

[8]D.B. Allison and others, "Alternative Treatments for Weight Loss: A Critical Review," *Critical Reviews in Food Sciences and Nutrition*, vol. 41 (2001), pp. 1-28. The authors reviewed bladderwrack (*Fucus vesiculosus)*, brindle berry (*Garcinia cambogia*), chitosan, chromium, conjugated linoleic acid (CLA), dehydroepiandrosterone (DHEA), ephedra, germander, ß-hydroxy-ß-methylbutyrate (HMB), plantain/psyllium, pyruvate, St. John's wort, and sunflower.

weight reduction.[9] Other smaller studies have shown similar results for ephedra.[10]

Adverse Effects, Contraindications, and Interactions Are Associated with Weight Loss Supplements

Available research on weight loss supplements, though limited, in general suggests that some supplements are associated with both minor and potentially serious adverse effects. Further, many supplements are contraindicated for individuals with some underlying health problems. That is, there are specific dangerous side effects for persons with certain health conditions. In addition, a variety of weight loss supplements can have dangerous interactions with prescription and over-the-counter drugs that are being taken concurrently. However, just as with research on efficacy, few systematic studies exist on the negative health consequences of particular weight loss supplements. Adverse effects, contraindications, and interactions that have been associated with some of the more commonly used weight loss supplements are shown in the appendix.

The side effects associated with weight loss supplements are generally mild and may include unpleasant digestive symptoms, insomnia, or rash. However, for some supplements there may be more serious adverse effects. For example, dehydroepiandrosterone (DHEA) may increase the risk of some hormone-related cancers. Both aloe taken internally, such as in a dieter's tea, and chromium may also increase the risk of cancer. FDA has identified illnesses and injuries reported to be associated with the use of selected weight loss supplements, including yohimbe, which has been associated with renal failure, seizures, and death, and ephedra, which has been associated with seizures, heart attacks, psychosis, stroke, and death.

Use of some weight loss supplements has been found to be contraindicated, or inadvisable, for persons with certain preexisting medical conditions. For example, bitter orange (*Citrus aurantium*) should be avoided by persons with certain heart conditions. DHEA may worsen prostate hyperplasia.[11] Neither herbal laxatives found in dieter's

[9]C.N. Boozer and others, "Herbal Ephedra/Caffeine for Weight Loss: A 6-Month Randomized Safety and Efficacy Trial," *International Journal of Obesity*, vol. 26 (2002), pp. 593-604. This study focused on otherwise healthy adults who were overweight or obese, and excluded from review persons with insulin-controlled diabetes, high blood pressure, active heart disease, or other illnesses.

[10]F. Greenway, "The Safety and Efficacy of Pharmaceutical and Herbal Caffeine and Ephedrine Use as a Weight Loss Agent," *Obesity Reviews*, vol. 2 (2001), pp. 199-211.

[11]Benign prostatic hyperplasia is the abnormal growth of benign prostate cells.

teas nor fiber should be used by persons with intestinal obstructions. Fiber and gymnema may affect persons with diabetes. These risks are of particular concern because serious health conditions, such as hypertension and diabetes, often go undiagnosed.[12] Consumers who have undiagnosed medical conditions and inadvertently use contraindicated dietary supplements may expose themselves to considerable risk.

Using weight loss supplements along with certain prescription medications and certain foods poses an additional risk. For example, fiber may alter the effects of some medications. Other supplements, such as DHEA, may duplicate the effects of prescription medications. Similarly, aloe and chromium affect blood sugar levels and may require altering the dosage of medication for diabetes. And many supplements, such as fiber, green tea, and guggul, may alter the effects of anticoagulant medications. Yohimbe and St. John's wort should not be used with certain foods (such as red wine, liver, and cheese) because they may cause a toxic reaction, and chitosan may affect the absorption of certain vitamins. The possibility of such interactions is of particular concern because it has been reported that more than 18 percent of those who use a prescription drug also use a dietary supplement, and further, about 60 percent of people who use dietary supplements do not discuss their supplement use with their doctors.[13]

Product Contamination and Content Variation May Pose Health Risks

Contaminated supplements and those with different amounts of active ingredients than indicated on the labels, or different active ingredients altogether, can pose significant health risks to consumers. Research has found supplements contaminated with pesticides or heavy metals, some of which are probable carcinogens and are toxic to the liver and kidneys. One commercial laboratory found contamination in samples of the weight loss supplements St. John's wort and chromium. For dietary supplements in general, the same laboratory found that 24 percent of the 62 herbal products it tested, particularly those containing ginseng, and 4 percent of

[12]It has been estimated that more than one-third of those with hypertension or high blood pressure and up to one-half of those with diabetes are unaware of their condition.

[13]D.M. Eisenberg and others, "Trends in Alternative Medicine Use in the United States, 1990-1997," *Journal of the American Medical Association*, vol. 280, no. 18 (1998), pp. 1569-75; and D.W. Kaufman and others, "Recent Patterns of Medication Use in the Ambulatory Adult Population of the United States," *Journal of the American Medical Association*, vol. 287, no. 3 (2002), pp. 337-344.

the 68 nonvitamin, nonmineral supplement products it tested were contaminated in some way.

Amounts of active ingredients can vary from what is indicated on a product label. Too much of an active ingredient may increase the risk of overdose for some consumers. Studies of DHEA, ephedra, and St. John's wort found that a number of products have substantially more active ingredient than indicated on the label. One brand of DHEA was found to contain 150 percent of the amount of active ingredient indicated. A study of ephedra showed that one product contained as much as 154 percent of the amount indicated. Too little of an ingredient can also pose a risk. For example, one chromium product tested by a commercial laboratory had less than 5 percent of its claimed amount of chromium. Because chromium can affect insulin and blood sugar levels, diabetics taking products containing chromium may attempt to adjust their medication dosage to compensate. However, if the chromium product does not contain the stated amount of active ingredient, the consumer may over- or undercorrect his or her dosage.

Further, products may contain active ingredients not on the label. In 2002, the International Olympic Committee (IOC) found that of 634 nutritional products tested, 15 percent contained ingredients banned by the IOC but not listed on product labels. Of the countries whose products were tested, the United States had the most products—19 percent—that contained ingredients that had been banned and were not listed on product labels.

Multiple-Ingredient Products Pose an Unknown Risk

Of particular concern to some federal officials is the widespread prevalence of multiple-ingredient weight loss supplements. Rarely do weight loss supplements contain just one active ingredient. In fact, multiple-ingredient products account for 85 percent of the weight loss supplement market. We found products containing as many as 22 active ingredients, all of which are classified as dietary supplements. In considering the scientific literature relevant to weight loss supplements, we found that although the majority of products marketed for weight loss contained more than one active ingredient, the majority of the research and evidence of adverse events is reported for each individual ingredient, not for multiple-ingredient products. FDA officials reported that there is little systematic research on individual ingredients and virtually none on multiple-ingredient products, with the possible exception of ephedra with caffeine. With multiple-ingredient products, potentially dangerous interactions may be more likely, as has been suggested with the combination of ephedra and caffeine, both stimulants.

It is more difficult to study the safety and efficacy of multiple-ingredient products because each product may have a different combination of ingredients, meaning that each individual product would need to be studied. Further, the amounts of ingredients in a product may be unknown if the product contains a "proprietary blend" of various ingredients. Proprietary blends must list ingredients but are not required to specify the amount of any individual ingredient. Finally, it is harder to identify patterns in the adverse events associated with multiple-ingredient products and attribute the events to either an individual ingredient or a combination of ingredients. A study found that in 95 percent of the adverse events reported to FDA for products containing chromium, the products also contained as many as 11 additional ingredients, any of which may have been responsible for the adverse event. It is also possible that it is the interaction of these ingredients that is responsible for the adverse events.

Limited Federal Efforts Have Focused More on Oversight of Advertising and Labeling than on Oversight of Safety

Federal oversight, research, and education efforts to protect and inform consumers about the potential risks associated with the use of some weight loss supplements have been limited. They have focused almost entirely on marketing issues such as advertising and labeling, rather than on safety issues associated with particular weight loss supplement ingredients. These efforts include carrying out enforcement activities against companies, funding research to evaluate weight loss supplements, and providing educational materials on potentially dangerous ingredients and fraudulent product claims. Since 1995, FTC, which generally oversees the advertising of weight loss supplements, has taken 30 actions related to supplements. FDA, which regulates the manufacturing and labeling of weight loss supplements, has taken 16 actions against manufacturers in the same period. FDA has faced difficulty in addressing safety concerns and has been slow to issue GMPs for dietary supplements. Although federal agencies have not given priority to research on weight loss supplements, they do provide some educational material to consumers.

FTC Has Focused Its Oversight and Enforcement Efforts on Advertising

FTC staff told us that the agency has taken legal action in 30 cases involving the advertising of weight loss supplements since 1995, after DSHEA went into effect. These actions resulted in more than $21.5 million in monetary relief and consumer redress. In addition, as of June 2002, FTC staff reported that they had a significant number of investigations pending against different manufacturers of weight loss supplements. In 2000, Enforma Natural Products agreed to a settlement with FTC regarding deceptive claims for two products and agreed to pay $10 million in consumer redress. The products, a chitosan-based product called "Fat

Trapper" and a pyruvate product named "Exercise In A Bottle" made claims such as

- "you can eat what you want and never, ever, ever have to diet again,"
- "you can enjoy all these delicious foods like fried chicken, pizza, cheeseburgers, even butter and sour cream, and stop worrying about the weight," and
- "foods you can eat when you crave them without guilt, without worry, and it's all because of a few little capsules."

However, in 2002, the company was still marketing the products in question. Since the filing of the final judgment in that case, FTC attorneys have filed two contempt actions against Enforma to enforce the provisions of the court's order. In 1999, FTC action was upheld in a case against SlimAmerica for its "Super-Formula," consisting of three different pills, containing chromium picolinate, hydroxycitrate (HCA), chitin, and konjac glucomannan (a soluble fiber).[14] The company was ordered to pay more than $8.3 million in consumer redress. In addition, the president and vice president of the company were ordered to post a $5 million and a $1 million performance bond, respectively, prior to engaging in any business related to weight loss products or services.

To help manufacturers better understand the advertising restrictions and requirements for dietary supplements, FTC issued a guide for advertising dietary supplements in November 1998. In addition, FTC conducts outreach to the industry regarding responsible advertising.

FDA Has Focused Its Oversight and Enforcement Efforts on Labeling

FDA is involved in varied activities to protect consumers of weight loss supplements, including enforcement actions against manufacturers for improper labeling and publication of a proposed rule regarding ephedra dosing. FDA has taken 16 enforcement actions since 1995 against the manufacturers of dietary supplements marketed with weight loss claims, and the majority of these have been for products that are improperly labeled as dietary supplements. For example, FDA determined in 1999 that Triax Metabolic Accelerator, labeled as a dietary supplement, was an unapproved new drug that contained a potent thyroid hormone that could cause heart attacks and strokes. The manufacturer agreed to stop

[14]These products claimed they would "'blast' up to 49 pounds off in only days, 'obliterate' five inches from waistlines, and 'zap' three inches from thighs—all without the need to diet or exercise."

distributing products containing the specified ingredient. In 2001, FDA took action resulting in the seizure of $2.8 million worth of AMP II Pro Drops, an unapproved drug product that contained ephedrine from a nonherbal source but was labeled as a dietary supplement. The manufacturer agreed in 2002 that it would not manufacture and distribute such products in violation of the law. In June 2002, FDA sent six more warning letters to companies that were also marketing nonherbal ephedrine products as dietary supplements.

In fiscal year 2002, FDA has allocated $1.4 million to support enforcement initiatives against manufacturers of dietary supplements making unsubstantiated labeling claims. From February 1997 through January 2002, FDA issued seven warning letters to manufacturers of weight loss products, focusing mainly on the labeling of these products. Five of these warnings were for products labeled as alternatives to the prescription drugs fenfluramine and/or phentermine, also known as Fen-Phen. These actions were taken because labels for dietary supplements cannot contain references to prescription drugs.

The only enforcement action FDA has taken on the basis of safety concerns specific to weight loss supplement ingredients came in 2001, when the agency warned consumers not to use LipoKinetix because of multiple reports of liver injury or failure while using the product. This product contained, among other things, caffeine and yohimbe. In addition, the agency issued a letter to health care professionals and the distributors of the product alerting them to the product's risks and asking distributors to voluntarily remove the product from the market.

To date, the most concerted attempt taken by FDA to protect consumers of weight loss supplements has been its effort to regulate dietary supplements containing ephedra. In 1997, FDA published a proposed rule regarding the dosing and labeling of products containing ephedra. After public comment and following our report on the subject that was critical of the science FDA used to develop some of its proposed rule,[15] the agency withdrew the parts of the proposed rule on dosing; the remaining elements focus on warnings and combinations with other ingredients. In June 2002, the Secretary of Health and Human Services announced that HHS was funding a comprehensive review of the existing science on ephedrine

[15] GAO/HEHS/GGD-99-90.

alkaloids as input to the proposed rule. This study is supported through the Agency for Healthcare Research and Quality.

FDA Has Faced Difficulty in Addressing Safety Concerns

FDA has been hindered in its ability to address safety concerns with weight loss supplements by weaknesses in its adverse event reporting system. Further, its authority to address potential safety concerns for weight loss supplements is different from that for drugs.

Weaknesses in the adverse event reporting system include difficulty in detecting patterns of events, as well as in obtaining voluntary adverse event reports. Adverse event reports are often incomplete and contain inconsistent information. Officials reported that it is easier to identify patterns with over-the-counter drugs and pharmaceuticals than with dietary supplements because there is a better understanding of the biological mechanisms of action from preclinical testing of these drug products and because manufacturers of such products that have approved applications are required to report adverse events to FDA. In contrast, it can be difficult to detect patterns for serious adverse events for dietary supplements in part because of the absence of preclinical testing. Nevertheless, HHS has reported that a pattern of potentially related events has been identified from adverse event reports for products containing ephedra, although questions remain on the strength of the products' association to the adverse events reported to FDA. The voluntary, or passive, nature of the adverse event reporting process for dietary supplements contributes to the difficulty in establishing causal connections. One manufacturer received more than 1,200 complaints of adverse events for a weight loss supplement containing ephedra, but, because there is no reporting requirement for dietary supplements, it did not forward any of these reports to FDA. The HHS Inspector General reviewed the adverse event reporting system in April 2001.[16] In response to that review, FDA is developing a new reporting system with an emphasis on dietary supplements, which should be available in mid-2003. Agency officials stated that the new system will enhance FDA's ability to capture data and follow up on event reports, but reporting will remain voluntary.

Although agency officials stated that the criteria they use to review adverse events reported for dietary supplements and for over-the-counter

[16]HHS, Office of Inspector General, *Adverse Event Reporting for Dietary Supplements: An Inadequate Safety Valve*, OEI-01-00-00180 (Washington, D.C.: April 2001).

or prescription drugs are the same, the authority to regulate dietary supplements, and to take action on safety concerns, is different from that for drugs. When FDA has health concerns about an over-the-counter ingredient, or combination of ingredients, the agency may determine that it is not generally recognized as safe and effective, and may issue a regulation or take other action to prohibit further marketing. FDA is not required to find that an over-the-counter drug is unsafe or dangerous to remove it from the market. In the case of dietary supplements, more significant safety concerns would have to be identified. For example, FDA is authorized to take regulatory action against a dietary supplement if its use would present a significant or unreasonable risk of illness under recommended conditions of use. If FDA were to take such action, however, it must be prepared to prove its allegations either in an administrative hearing or court. Unlike its regulation of over-the-counter drugs, FDA has the burden of proving that a dietary supplement presents a significant or unreasonable risk before it can be taken off the market.

These differences in regulatory standards are reflected in differences in actions taken for similar or identical ingredients. Specifically, FDA has concluded that two categories of products are not generally recognized as safe and effective and cannot be marketed for over-the-counter use. These categories of products, however, may be used in dietary supplements. First, in September 2001, FDA ruled that over-the-counter drugs containing ephedrine and related alkaloids in combination with an analgesic or stimulant would be removed from the list of ingredients generally recognized as safe and effective, and thus could no longer be marketed as drugs. There is no similar rule prohibiting the manufacture and marketing of dietary supplements containing herbal ephedra in combination with herbal analgesics or stimulants. Second, in May 2002, the agency issued a rule that the stimulant laxative ingredients aloe and cascara sagrada in over-the-counter drugs are not generally recognized as safe and effective and cannot be marketed. However, these ingredients may be marketed in dietary supplements and are commonly found in dieter's teas.

FDA Has Been Slow to Finalize Good Manufacturing Practice Regulations

FDA has drafted GMP regulations for dietary supplements but has been slow to finalize these regulations. GMPs would standardize manufacturing, packaging, and holding practices for dietary supplements. The agency published an advance notice of proposed rule making for GMPs in February 1997. A draft proposed rule was developed during the summer of 2000. The new administration was given the opportunity to review the proposed rule, and HHS as well as the Office of Management and Budget had significant comments. Currently, the rule is in administrative

clearance with HHS. As we have previously stated,[17] publication of final GMP regulations will improve FDA's enforcement capabilities, since DSHEA provides that dietary supplements not manufactured under conditions that meet GMPs would be considered adulterated.[18] FDA would be able to take enforcement action against the manufacturers of adulterated products if they were subject to GMP regulations.

Meanwhile, four private efforts are under way to review the manufacturing practices of supplement makers and evaluate the ingredients in dietary supplement products. Specifically, the U.S. Pharmacopeia, Good Housekeeping Institute, consumerlab.com, and NSF International each have voluntary programs in which manufacturers submit products and pay a fee to get their products reviewed. These programs do not look at product safety, but rather focus on label accuracy. In addition, the National Nutritional Foods Association, a trade association representing manufacturers of dietary supplements, has two programs to help ensure product quality.[19]

Weight Loss Supplements Have Not Been a Federal Research Priority

NIH officials reported that research on weight loss supplements is not a priority and the agency has not made any formal program announcements or requests for proposals to study weight loss supplements. However, the agency has sponsored limited research on weight loss supplements through two of its research institutes and centers. In fiscal year 2001, NCCAM spent $627,000 of its annual budget of $89.1 million on research of weight loss supplements.[20] The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) currently supports investigator-initiated research on conjugated linoleic acid (CLA) and chromium picolinate.[21] In addition, NIH has supported other research on ingredients found in weight

[17]GAO-01-1129.

[18]Generally, adulteration refers to products that may contain contaminants or are otherwise unsafe.

[19]The GMP certification program for the association's members uses third-party inspectors to ensure that products meet their purported quality and entitles the manufacturers to use the association's GMP certification mark. The quality assurance program provides for random, independent tests of products.

[20]NCCAM studied ephedra and caffeine, the mechanics of ephedra, and the insulin regulation properties of ginkgo biloba.

[21]These studies were funded for a total of $228,710 in fiscal year 2001 by ODS and the Office of the Director.

loss supplements, though not in studies specifically related to weight loss. Data from this research may help address the safety of some of these supplements. Further, the National Institute of Environmental Health Sciences and the HHS National Toxicology Program are conducting toxicological research on weight loss supplements in animals to further understand their potential adverse effects in humans.

ODS officials reported that the office had been asked by the Congress to work with other federal agencies to study the safety and efficacy of dietary supplements in general and develop a research agenda on the safety and efficacy of ephedra, specifically. It is starting with a systematic evidence-based review of ephedra. This review is funded by ODS and NCCAM through the Agency for Healthcare Research and Quality's Evidence-based Practice Program, and the findings are scheduled for release in the fall of 2002.[22] ODS is also working with other agencies and trade associations to develop analytic tools and standards for testing supplements. In addition, the National Heart, Lung, and Blood Institute is working with ODS to offer a workshop on weight loss supplements to review scientific evidence and identify research gaps.

FDA has funded the Institute of Medicine's Food and Nutrition Board to develop a "Framework for Evaluating the Safety of Dietary Supplements" that will allow the agency to prioritize further research on dietary supplements, including weight loss supplements, by identifying which ingredients are of the greatest concern. The framework will also establish a methodology for doing rigorous safety evaluations. A preliminary framework is currently undergoing review, and the final report is expected to be available by the end of 2002.[23]

Federal Agencies Provide Some Educational Materials to the Public

FTC and FDA have programs designed to provide the public with information about healthy weight loss practices, including weight loss supplements. FTC has Operation Waistline, which, among other activities, highlights fraudulent claims made by the manufacturers and distributors of weight loss products. FTC also has a number of links on its Web site encouraging consumers to beware of certain advertising claims that may

[22]This study, performed under contract with RAND, was supported with $380,000 from ODS and $100,000 from NCCAM.

[23]Institute of Medicine, "Proposed Framework for Evaluating the Safety of Dietary Supplements" (draft) (Washington, D.C.: National Academy Press, July 2002).

be associated with some weight loss products. In addition, in an effort to demonstrate to consumers how Web sites selling such products may be misleading, FTC has developed a Web site designed to look as if it is selling a real weight loss supplement. However, once a customer tries to make a purchase, the Web site informs the customer that he or she would have been scammed had this been a "real" Web site. According to agency officials, this Web site has been visited more than 9,000 times since 1998. In general, FDA makes information about supplements available to the public through its Web site and media announcements. Two publications, "Tips for the Savvy Supplement User" and "An FDA Guide to Dietary Supplements," together provide a general overview of the dietary supplement industry. FDA provides updated information with periodic news and warnings about specific products.

State Consumer Protection Efforts Include Legislation and Litigation

Some states have adopted a variety of statutes and regulations to protect consumers from potentially dangerous supplement ingredients and fraudulent supplement marketing practices. In addition, there have been state and local lawsuits aimed at the manufacturers of some weight loss supplements over product claims and private lawsuits over injuries.

State Statutes and Regulations

States have adopted statutes and regulations specific to the sale of certain weight loss supplements. Most of these states' actions control the sale of ephedra; the exception is California, which requires a warning label for products containing herbal ingredients with a laxative effect, such as senna, aloe, buckthorn, cascara, grangula, and rhubarb root. The majority regulate ephedra in connection with the regulation of controlled substances. Generally, ephedra is regulated to deter its use in the illegal manufacture of the controlled substance methamphetamine, rather than its use as a dietary supplement. Some states have prohibited ephedra sales to minors, some have declared it an illegal drug, and others have adopted regulations on how and to whom it can be sold[24] (see table 1).

[24]In addition, the National Football League, NCAA, IOC, and U.S. Olympic Committee ban the use of ephedra and its active ingredient, ephedrine.

Table 1: State Statutes or Regulations on Ephedra in Effect as of July 2002

State	Ephedra in controlled substance statutes or regulations	Requirements			Comments
		Dosing limits[a]	Warning label	Cannot sell to minors	
Arkansas	X[b]				Regulation applies to all products containing ephedra as the sole active medicinal ingredient or in combination with therapeutically insignificant quantities of another active medicinal ingredient or ingredients.
Hawaii	X[c]	X			
Michigan	X[c]	X	X[d]	X	
Nebraska		X	X[e]		Previously, Nebraska had banned the sale of ephedra.
Ohio	X[c]	X	X[d]	X	
Oklahoma	X[c]	X	X[d]		
South Dakota	X[b]				Dietary supplements containing ephedrine or "ma juang" (sic) are controlled substances and cannot be sold legally without a prescription.
Texas			X[e]	X	
Virginia				X	Any product combining caffeine and ephedrine sulfate cannot be sold to minors without a prescription.
Washington		X			Use of ephedra requires a prescription if dosing limit requirements are not met.

[a]Dosing generally limits serving size to 25 mg, for a total of not more than 100 mg per day.

[b]All products containing ephedra are considered controlled substances.

[c]Ephedra is exempted as a controlled substance providing certain requirements about dosing or warnings are met.

[d]Warnings state that improper use may be hazardous to one's health.

[e]Warnings generally suggest consulting a physician, using with caution for those with certain diseases, and discontinuing use if negative side effects are experienced.

Source: GAO analysis of state laws.

Texas has the most specific regulations for products containing ephedra concerning product content and labeling. In addition to the requirements stated in table 1, each batch of a product must be analyzed to ensure that it contains the amount of total ephedrine alkaloids listed on the product label. In addition, labels must include the amount of caffeine and other stimulants, cautions about use with caffeine, and FDA's toll-free telephone number for reporting adverse events.

Other states are considering legislation to regulate ephedra. For example, in May 2002, the California State Senate passed a bill that would ban the sale of ephedra to minors, require prominent warning labels, and include a toll-free telephone number to FDA so consumers can report adverse events. California also has proposed that school districts be required to provide students with information on the effects of and the dangers of ephedra. Massachusetts has proposed ephedra legislation that would limit dosing and require warning labels. Idaho's Board of Pharmacy has also proposed establishing labeling, content, and registration requirements for ephedra, as well as banning the sale to minors. Both New York and New Jersey have proposed legislation that would prohibit the sale of products containing ephedra to persons under age 18.

State, Local, and Private Lawsuits

Some state attorneys general and local district attorneys have sued marketers or manufacturers of weight loss supplements over marketing claims. One California county district attorney told us that since the mid-1990s, his office has prosecuted more than 30 consumer protection cases involving weight loss products, all of which were settled, with penalties ranging from $5,000 to $500,000. For example, this county sued Enforma (as did FTC, see above) and received $500,000 in civil penalties and costs, including a $100,000 penalty against its celebrity spokesperson. The Pennsylvania Attorney General has also settled with two companies. In one case, a product claimed numerous health benefits such as that consumers could lose 17 pounds in 1 month and that the product "reduces fat and calories automatically by carrying them out of your body before they could be absorbed." The distributor is prohibited from selling or delivering the product in the state, and agreed to offer full refunds and pay $2,000 in civil penalties and $1,500 in investigation costs. In the second case, the company claimed the product would "flush calories right out of your body" and that consumers could "eat all you want and still lose weight." The manufacturer agreed to stop making unsubstantiated claims, add disclosures to its product labels, and pay $2,000 in civil penalties and $3,000 in investigation costs.

Attorneys involved in private lawsuits reported that most private lawsuits alleging injuries from weight loss supplements are settled out of court and do not go to trial. However, in 2001, a jury awarded $13.3 million to a woman who suffered a debilitating stroke after taking a dietary supplement containing ephedra for weight loss. This particular product also contained synthetic stimulants that are not considered dietary supplements, and the manufacturer had received warnings about the product from FDA.

Conclusions

To date, federal activity on weight loss supplements has focused on oversight of marketing more than on oversight of safety. Federal activity has focused less on safety in part because FDA is largely dependent on voluntary reporting of adverse events for information on safety. It is also more difficult for FDA to identify patterns of safety concerns for dietary supplements than for drugs. FDA's authority to regulate dietary supplements is different from its authority to regulate drugs and it has a greater burden of proof to take action against supplements that may be unsafe. Because of these differences in regulatory authority, some weight loss products with similar or identical active ingredients may be marketed as dietary supplements, but not as drugs.

Further, research specific to weight loss supplements has not been a priority for federal agencies. There have been few systematic studies of weight loss supplements. Consequently, little is known about whether weight loss supplements are effective, but many of them have been reported to be associated with the potential for physical harm. However, as the upward trend in sales and use is expected to continue, more consumers may be at risk of adverse events related to use of the supplements. Consumers need scientifically accurate information about safety and efficacy to help guide their choices about weight loss supplements.

Mr. Chairman, this completes my prepared statement. I would be happy to respond to any questions you or other Members of the Subcommittee may have at this time.

Contact and Acknowledgments

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Appendix: Identified Adverse Effects, Contraindications, and Interactions Associated with Weight Loss Supplements

We focused our review on dietary supplements that are commonly used for weight loss.[1] For each supplement, we have listed in table 2 the adverse effects that have been reported to be associated with the supplement, conditions for which the supplement might be contraindicated, and prescription medicines and foods with which the supplement might have dangerous interactions. The sources we used to generate this table gathered information from laboratory, animal, and human studies. The evidence from human studies includes case reports, observational studies, and clinical trials. We have not independently validated these associations.

Table 2: Identified Adverse Effects, Contraindications, and Interactions Associated with Commonly Used Dietary Supplements Promoted for Weight Loss

Supplement	Identified adverse effects	Identified contraindications	Identified interactions
Bitter orange (*Citrus aurantium*)	Sensitivity to light and increased blood pressure.	Should be avoided by individuals with cardiovascular concerns such as hypertension.	
Bladderwrack (*Fucus vesiculosus*)	High doses and prolonged use associated with risk of iodine overdose and hyperthyroidism.	Should be avoided by individuals with hyperthyroidism. Long-term use is not recommended.	May have an additive effect with antihyperglycemic medications.
Brindle berry (*Garcinia cambogia*) (hydroxy citric acid)	High doses associated with gastrointestinal (GI) distress.	Should be avoided by individuals with diabetes and dementia syndromes.	
Caffeine (guarana, cola nut)	GI distress, nausea, dehydration, headaches, insomnia, nervousness, anxiety, muscle tension, heart palpitations, increased blood pressure, addiction, and possible genetic damage.	Should be avoided by individuals with gastric ulcers. High doses and long-term use are not recommended.	May strengthen the action of central nervous system stimulants that reverse depression.
Chromium	Mild GI distress, anemia, blood abnormalities, liver dysfunction, renal failure, memory loss, rhabdomyolysis, tissue damage, genetic damage, genetic mutation, and cancer.	Should be used with caution by individuals with a history of hypoglyclemia. Should be used only under medical supervision by individuals with a history of hyperglycemia or type II diabetes. High doses of chromium picolinate are not recommended.	May cause corticosteroid-induced diabetes when taken with corticosteroid medications.

[1]To be included in the table, a supplement had to be listed in at least two of the following sources as having a weight loss claim: supplementwatch.com; supplementinfo.com; *Nutrition Business Journal*, D.B. Allison and others, "Alternative Treatments for Weight Loss: A Critical Review," *Critical Reviews in Food Sciences and Nutrition*, vol. 41 (2001), pp. 1-28; and G. Eggar and others, "The Effectiveness of Popular, Non-prescription Weight Loss Supplements," *Medical Journal of Australia*, vol. 171 (1999), pp. 604-8.

Supplement	Identified adverse effects	Identified contraindications	Identified interactions
Conjugated linoleic acid (CLA)	GI distress and nausea.		Should not be used with medications, mineral oil, dietary supplements, or food additive s that prevent absorption of fats.
Dehydroepiandrosterone (DHEA)	Altered hormone profiles, increased facial hair, acne, scalp hair loss, oily skin, mood swings, aggressiveness, irritability, virilization in women and gynecomastia in men, a deepening of the voice, and menstrual cycle irregularities. Also associated with insomnia; headaches; nervousness; fatigue; low energy; decreased high density lipoprotein (HDL) cholesterol ("good cholesterol"); cardiac arrhythmias; liver abnormalities; hepatitis; and increased risk of heart disease, diabetes, stroke, and some hormone-related cancers.	Should be used only under medical supervision by individuals at risk for hormone-related cancer such as prostate, ovarian, endometrial, and breast cancer. Long-term use may worsen prostate hyperplasia. High doses are not recommended.	May alter the effects of antidepressants, estrogen and estrogen-like medications, anticoagulants, central nervous system stimulants, and diabetic/hypoglycemic medications.
Dieter's teas (containing aloe, buckthorn, cascara, castor oil, rhubarb root, senna, or other herbal laxatives)	GI distress, stomach cramps, pain, constipation, nausea, vomiting, and diarrhea (sometimes chronic), fainting, dehydration, electrolyte disorders, potassium deficiency, nephropathies, edema, accelerated bone deterioration, and cardiac arrhythmias. Aloe taken orally may increase risk of cancer.	Should be avoided by individuals with abdominal pain of unknown origin, diarrhea, dehydration, intestinal obstruction, and any inflammatory condition of the intestines (appendicitis, colitis, Crohn's disease, irritable bowel syndrome, or ulcerative colitis). Aloe should be avoided by individuals with hemorrhoids or kidney dysfunction. Rhubarb should be used with caution by individuals with a history of kidney stones. Use for more than 2 weeks is not recommended.	May alter the effects of antiarrhythmics, digoxin, digitalis, electrolytes, nonsteroidal anti-inflammatory drugs, and decrease the absorption of other oral medications. Potassium deficiencies associated with use of stimulant laxatives can lead to disorders of heart function and muscle weakness, especially with concurrent use of cardiac glycosides, diuretics, and corticosteroids. Aloe may lower blood sugar levels and alter the effect of diabetic/hypoglycemic medications. Senna decreases the absorption of estrogens.
Ephedra (*ma huang*)	Loss of appetite, nausea, vomiting, disturbances of urination, sweating, pupil dilation, insomnia, irritability, nervousness, dizziness, shortness of breath, elevated body temperature, tremor, muscle injury, nerve damage, severe headaches, memory loss, psychosis, increased blood pressure, heart palpitations, seizures, stroke, heart attack, and death. High doses associated with dependency.	Should be avoided by individuals with glaucoma, thyroid disease, diabetes, high blood pressure, or heart disease. Should also be avoided by individuals with difficulty in urination due to prostate enlargement. Should be used only under medical supervision by individuals with a kidney disorder, psychiatric disorder, or seizure disorder. Should discontinue use at least 24 hours prior to surgery.	May alter the effects of cardiac medications. Should not be used with other medications, including nonprescription allergy, asthma, cold/cough, weight control products, and antidepressants. Use of ephedra with monoamine oxidase (MAO) inhibitors strengthens the stimulant action of ephedra and may result in life-threatening fever, hypertension, and coma.

Supplement	Identified adverse effects	Identified contraindications	Identified interactions
Fiber (chitosan, psyllium, methylcellulose, glucomannan, pectin, or others)	GI distress including gas; bloating; intestinal cramps; abdominal distention; nausea; diarrhea; choking; and obstruction of the esophagus, throat, and intestines.	Should be avoided by individuals with a history of intestinal obstruction, fecal impaction, or narrowing of the gastrointestinal tract, and those who have difficulty controlling their diabetes. Should be used with caution by individuals with shellfish allergies and insulin-dependent diabetes (insulin and/or medication levels may need to be adjusted).	May alter the effects and decrease the absorption of diabetic/hypoglycemic medications, cholesterol-lowering medications, anticoagulants, digoxin, and other oral medications. High intake may decrease absorption of fat-soluble vitamins (A, D, E, and K) and carotenoids (such as beta-carotene, lutein, and zeaxanthin).
Green tea (catechins)	GI distress, decreased appetite, insomnia, nervousness, hyperactivity, increased blood pressure, increased heart rate, and gastric irritation. High doses associated with headache, heart palpitations, and vertigo.	Should be used with caution by individuals with renal disease, hyperthyroidism, susceptibility to spasm, anxiety, and panic disorder. Should be used only under medical supervision by individuals with peptic ulcers, cardiovascular disease, and blood clotting abnormalities. High doses should be avoided by individuals with irregular heartbeat. Should discontinue use at least 24 hours prior to surgery.	May alter the effects of anticoagulant medications and supplements (including vitamin E and ginkgo biloba), resulting in decreased platelet aggregation (blood clotting) and increased bleeding times.
Guggul (myrrh)	GI distress, diarrhea, nausea, and skin rash.	Should be used only under medical supervision by individuals with hyperthyroidism.	May alter the effects of thyroid medications, cholesterol-lowering medications, anticoagulants, antiplatelet medications, propranolol, and diltiazem.
Gymnema	GI distress. Extremely high doses associated with hypoglycemia.	Should be used only under medical supervision by individuals with active diabetes.	May alter the effects of oral hypoglycemics and insulin. Antidepressants, including St. John's wort and salicylates (white willow and aspirin), may enhance the effects of gymnema. Stimulants, including ephedra, may reduce its effectiveness.
HMB (ß-hydroxy-ß-methylbutyrate)			
5-Hydroxytryptophan (5-HTP)	Nausea, vomiting, diarrhea, loss of appetite, difficult breathing, pupil dilation, blurred vision, abnormally sensitive reflexes, loss of muscle coordination, and cardiac arrhythmias.	Should be avoided by individuals with any significant cardiovascular disease. Should be used only under medical supervision by individuals with cancerous tumors.	Should not be used with MAO inhibitors, other antidepressants (including herbal remedies such as St. John's wort), or prescription weight loss medications.
L-Carnitine	Nausea, vomiting, diarrhea, abdominal cramps, and seizures.	Should be used only under medical supervision by individuals with thyroid disease or seizure disorder.	

Supplement	Identified adverse effects	Identified contraindications	Identified interactions
Pyruvate	GI distress including nausea, gas, bloating, and diarrhea.	Should be used only under medical supervision by individuals with blood clotting abnormalities. Should discontinue use at least 14 days prior to surgery.	
St. John's wort	GI distress, nausea, loss of appetite, constipation, dry mouth, sensitivity to light, allergic reactions, skin rash, hives, tiredness, fatigue, insomnia, restlessness, dizziness, confusion, and fast or irregular breathing.	Should be avoided by individuals who are attempting to become pregnant (may be mutagenic and toxic to sperm), and individuals who have received organ transplants or are taking medications that decrease immune system activity. Should be used only under medical supervision by individuals with severe depression.	May alter the effects of oral contraceptives, decrease the effectiveness of HIV medications, immunosuppressants, digoxin, anticoagulants, chemotherapy, and asthma medications. May alter the effects of other prescription or over-the-counter medications. Should be used only under medical supervision when taking MAO inhibitors or other prescription antidepressants. Should not be used with tyramine-containing foods (certain wines, liver, and cheeses).
Vanadium	GI distress. High doses and long-term use associated with muscle cramps, depression, and damage to the nervous system and other organs.	Should be avoided by individuals with hyperglycemia, hypoglycemia, or diabetes.	
Yohimbe	Queasiness, vomiting, insomnia, headache, sweating, flushing, nervousness, tension, tremors, difficulty breathing, hallucinations, anxiety, psychotic episodes, increased blood pressure, increased heart rate, heart palpitations, and chest pain. High doses associated with decreased blood pressure, GI distress, and unpleasant central nervous system symptoms.	Should be avoided by individuals with low blood pressure, diabetes, high blood pressure, kidney disease, liver disease, chronic inflammation of the sexual organs or prostate gland, cardiovascular disease, women who could become pregnant, and elderly persons. High doses and long-term use are not recommended.	Should not be used with antidepressant medications or supplements, nasal decongestants, weight loss supplements with ephedrine, or tyramine-containing foods (certain wines, liver, and cheeses). May increase the effect of MAO inhibitors and hypotensive drugs. May alter the effects of psychopharmacological herbs.

Note: We do not include any adverse effects or contraindications specific to infants, children, pregnant women, or nursing mothers.

Sources: *Physicians' Desk Reference for Herbal Medicines*, 2nd ed. (Montvale, N.J.: Medical Economics Company, Inc., 2000); *Physicians' Desk Reference for Nutritional Supplements* (Montvale, N.J.: Medical Economics Company, Inc., 2001); M. Blumental, ed., *The Complete German Commission E Monographs: Therapeutic Guide to Herbal Medicines* (Boston, Mass.: American Botanical Council, 1998); K. Bruss, ed., *American Cancer Society's Guide to Complementary and Alternative Cancer Methods* (Atlanta, Ga.: American Cancer Society, 2000); M. McGuffin and others, eds., *American Herbal Products Association's Botanical Safety Handbook* (Boca Raton, Fla.: CRC Press LLC, 1997); and D.B. Allison and others, "Alternative Treatments for Weight Loss: A Critical Review," *Critical Reviews in Food Sciences and Nutrition*, vol. 41 (2001), pp. 1-28. See also www.fda.gov/fdac, www.supplementwatch.com, and www.supplementinfo.org.