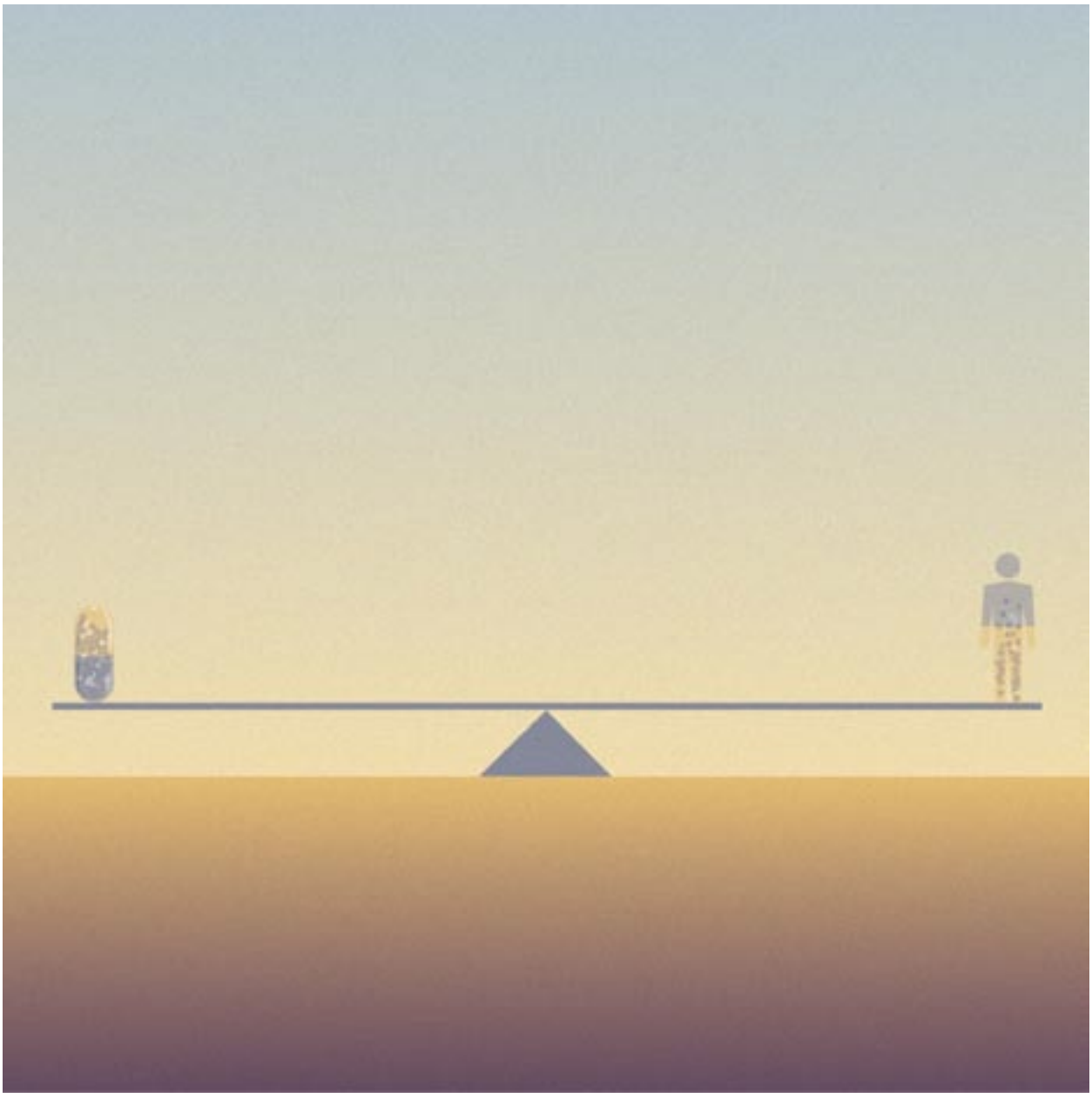
Dietary Supplements

Balancing Consumer Choice & Safety



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Preface

The New York State Task Force on Life & the Law was convened by gubernatorial mandate in 1985, and has served since then as a resource in medical ethics for New York State government. In fulfilling its mandate, the Task Force has developed recommendations for public policy on a host of issues at the interface of law and medicine, including: the determination of death; withholding and withdrawing life-sustaining treatment; organ transplantation; surrogate decision-making; physician assisted suicide; assisted reproductive technologies; and genetic testing. Task Force recommendations have taken various forms, including proposals for law, regulation, and public education. Many Task Force recommendations have become New York State law, and have also served as models for legislation in other states.

This report examines dietary supplements, focusing on their safety, use by consumers, and regulation at the federal and state levels. This topic is markedly different from previous Task Force reports, which have addressed more classic issues in medical ethics, primarily at the beginning and end of life. However, the Task Force finds troubling ethical issues within the domain of dietary supplements. Informed choice is a significant issue within medical ethics, and has been a major focus of many Task Force reports. Informed choice depends upon access to adequate and accurate information, and occurs within a context of beliefs about the safety of available options.

Consumers may presume that all dietary supplements are safe and the Task Force believes that this confidence is unwarranted. The presumption rests on the belief that dietary supplements are safe because they are "natural," because the federal government closely monitors them, and because health professionals are well informed about the risks and benefits of dietary supplements. Each of these bases for the presumed safety of dietary supplements is flawed, as we examine in this report. The Task Force addresses the relative lack of sound scientific data on dietary supplements, their limited government regulation, and the current deficits in education regarding dietary supplements. The Task Force recommendations call for greater attention to each of these three areas to help New York consumers make well-informed and safer choices.

Acknowledgements

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Executive Summary
Dietary Supplements: Balancing Consumer Choice & Safety

The dietary supplement industry is a multi-billion-dollar enterprise in the United States, and dietary supplement manufacturers and distributors enjoy nearly unfettered access to consumers in New York and throughout the United States. Millions of American consumers ingest these supplements; recent surveys report nearly half of the American adult population routinely use dietary supplements.[1]

The consumer turns to dietary supplements to maintain or improve health—perhaps to supplement a vitamin deficiency, lose weight, or support organ function—often believing them to be more natural, potent or pure than food or pharmaceuticals. Dietary supplements with a broad range of health claims are widely available, and the consumer may think that they have been proven effective. Dietary supplement labels need not list risks or contraindications, and the consumer may assume that supplements are safe. In each case the consumer may be wrong.

Dietary supplements are defined under federal law as products that are intended to "supplement the diet" and that contain certain "dietary ingredients" such as vitamins, minerals, herbs, and amino acids.[2] Dietary supplements are regulated as a class of foods, not as drugs. Like foods—and unlike drugs—most dietary supplements are not screened for safety and effectiveness by the U.S. Food and Drug Administration (FDA). Federal law does not permit dietary supplement labels to contain drug claims, such as assertions that supplements are intended to treat, diagnose, mitigate, prevent or cure diseases (absent prior government approval in specific cases). Yet the airwaves are filled with advertisements touting the health-promoting properties of dietary supplements, without mention of risk. The line between permissible and impermissible health claims for supplements is not always clear to the consumer, who naturally may misconstrue the apparent bounty of medicinal-sounding risk-free benefits.

But while many supplements may be beneficial, they are not without risks. As discussed in Chapter 3 of this report, these risks include the following:

· Certain dietary supplements have been associated with severe side effects (e.g., kava with liver failure, aristolochic acid with kidney failure);

· Certain dietary supplements have known side effects comparable to those associated with pharmaceuticals;

· Persons "self-medicating" with dietary supplements may delay necessary effective conventional medical treatment, and exacerbate disease;

· Dietary supplements may interact with common prescription and over-the-counter medications;

· The misperception that "if a little is a good, more has to be better" can lead consumers to mega-dose, risking toxic effects even from "safe" dietary supplements.

It is hoped this report is a first step toward giving New York consumers the power to make more informed choices about dietary supplements. The Task Force is recommending state-level actions because current federal oversight of dietary supplements is inadequate. Measures by New York State are warranted until the federal government implements adequate standards and enforcement for manufacturing, safety, and effectiveness.

The current scope of federal oversight of dietary supplements was established primarily by the Dietary Supplement Health and Education Act (DSHEA) of 1994.[3] Among the provisions of DSHEA is an expanded definition of dietary supplements and dietary ingredients; guidelines for advertising and marketing of dietary supplements; requirements for dietary supplement product labels, and the authority for the FDA to establish good manufacturing practices for dietary supplement manufacturers.

The supplement industry has long maintained that the FDA has ample authority under DSHEA to regulate supplements and even remove them from the market when necessary. The Task Force strongly disagrees. Consider ephedra, once the dietary supplement industry's biggest moneymaker, whose sale the FDA finally restricted a decade after serious health concerns emerged. The FDA was aware of serious adverse events associated with ephedra as early as 1994.[4] Yet not until 2004 did the FDA determine that ephedra posed an "unreasonable risk" of illness or injury when used under its suggested or ordinary conditions of use, and issued a regulation that essentially banned the sales of ephedra supplement products nationwide.[5] Then in April 2005, a federal district court questioned the method by which FDA had shown unreasonable risk, and struck down the ban, at least as it applied to certain "low-dose" ephedra products.[6]

The lesson of ephedra is that states must be prepared to act when the FDA does not, or cannot. Indeed, a number of states, concerned by delays at the federal level, acted independently to regulate ephedra. In New York, Governor George E. Pataki signed into law a statewide ban on dietary supplements containing ephedra, effective in October 2003, citing his concern for the health and well-being of New Yorkers.[7]

The Task Force supports state action in light of the following facts, among others:

· DSHEA does not require dietary supplement manufacturers to submit safety data to the FDA before their products are sold to consumers.

· DSHEA does not require manufacturers to report adverse events associated with dietary supplements to the FDA or any other entity.

· DHSEA does not require manufacturers to include risk information on product labels, even for dietary supplements that have been associated with serious adverse events.

The federal government has the ability to address these problems. Unless and until these problems are remedied at the federal level, however, New York State action is required.

* * *

The following recommendations contemplate an Expert Committee to consider specific dietary supplements in depth, and to advise the Department of Health on provisions for ensuring the safety of New York consumers by mandating appropriate collection of data from adverse events and research, and by permitting an efficient response to evidence of risk through changes in labeling and retail restrictions as needed. An education campaign is also recommended to fill the gaps in public information.

Recommendation I

The New York State Commissioner of Health should create an Expert Committee within the Department of Health to evaluate the safety and efficacy of dietary supplements on an ongoing basis. The Expert Committee will assess available data and make specific recommendations to the Commissioner of Health.

Data on the safety and efficacy of dietary supplements emerge continually from scientific research, adverse event reports, and other sources. Therefore, the Task Force recommends that an Expert Committee be created under the auspices of DOH to collect, evaluate, and retain all available data on the safety and efficacy of dietary supplements. The committee will also evaluate dietary supplements to determine what (if any) danger they present to the public. These evaluations will result in specific policy or regulatory recommendations to the Commissioner of Health. These recommendations might range from issuing a public advisory to banning the sale of a particular dietary supplement or dietary supplement ingredient.

The Expert Committee should consider the following policies supported by the Task Force based on current information:

i. Institute mandatory reporting by dietary supplement manufacturers and distributors of adverse events associated with dietary supplements, with continued support for voluntary reporting by consumers, health care practitioners, and others.

The FDA defines an adverse event as an incident of illness or injury that may be associated with a dietary supplement (or a range of other products), whether or not there is a clear cause/effect relationship between the adverse event and the product. A serious adverse event is one that results in a death, life-threatening illness, hospitalization, disability, congenital anomaly, or medical intervention to prevent permanent injury or damage.[8]

The FDA system for tracking adverse events related to dietary supplement use is inadequate. By its own estimate, the FDA tracks few adverse events (as few as one percent in 2000).[9] From 1994 to 1999, the FDA received less than ten reports of adverse events from dietary supplement manufacturers. Since they are not required to collect such information, some manufacturers had no data on adverse events, while others had information that they did not share with the FDA.[10]

The Task Force believes that mandatory reporting of serious adverse events related to dietary supplement use will enhance the ability of DOH to detect patterns of illness or injury resulting from individual products that may be adulterated, contaminated, or otherwise dangerous. In addition to mandatory reporting by manufacturers and distributors doing business in New York, retailers, consumers, and health care practitioners should be encouraged to report all dietary supplement-related adverse events that occur in New York State to the FDA.

The Expert Committee should consider the following policies supported by the Task Force based on current information:

ii. Create a state-level registry of dietary supplement manufacturers and distributors doing business in New York State, or other equivalent mechanism for 1) assuring compliance with mandatory reporting of adverse events, and 2) facilitating communication with dietary supplement manufacturers and distributors.

The Expert Committee should consider the most effective means for the state to ensure compliance with mandatory adverse event reporting. One possible solution would be the establishment of a registry of those entities from which reporting is required.

The Expert Committee should consider the following policies supported by the Task Force based on current information:

iii. Obtain statutory authorization for the Commissioner of Health to require, by regulation, specific labeling of dietary supplement packaging by manufacturers on such terms as the Commissioner may deem reasonable.

Current federal dietary supplement labeling regulations fail to ensure that sufficient information is provided to facilitate consumer understanding.[11] State-level labeling mandates can address deficits by 1) alerting consumers that particular products have not been determined to be safe and/or efficacious, and 2) informing consumers of risks that are reasonably suspected.

The Expert Committee should consider what the Task Force believes are necessary steps to ensuring the flow of accurate and sufficient information to consumers. First, the power to require dietary supplement labeling should be explicitly assigned by the Legislature to the Commissioner of Health. The Task Force recommends that the Commissioner of Health mandate that dietary supplement products that have not been proven safe during pregnancy and lactation carry a warning label. Also recommended is the labeling of specific products that have known associated risks. Finally, the Expert Committee should consider recommending that the Commissioner mandate that the labels of all dietary supplement products sold in New York State bear the FDA MedWatch toll-free telephone number, to facilitate adverse event reporting.[12]

The Expert Committee should consider the following policies supported by the Task Force based on current information:

iv. Obtain statutory authorization for the Commissioner of Health to ban the sale to minors or to all persons in New York State of specific dietary supplements found by the Commissioner to be unsafe.

The Task Force is not recommending actions directed at specific dietary supplements. However, in the course of research, the Task Force evaluated a number of dietary supplements that might be deemed unsafe. As two initial projects in this areas, the Expert Committee should (1) review the evidence for banning the sale to minors of dietary supplements that are marketed as legal alternatives to illegal drugs, and (2) review data and consider banning the sale of aristolochic acid, comfrey, and kava to all consumers in New York State.

Recommendation II

The Department of Health should undertake a major public health education campaign on dietary supplements, with variations specifically directed to different target groups.

The public education campaign will provide information about dietary supplement risks and benefits, as well as guidance for consumers in deciding whether or not to purchase dietary supplements, and how to respond to adverse events arising from dietary supplement use. Portions of the campaign should be tailored to different target audiences, including physicians and other health care professionals, complementary and alternative medicine practitioners, coaches, educators, parents, and adolescents.

* * *

These recommendations strike an appropriate balance between two legitimate state purposes: respecting consumer freedom to purchase potentially beneficial products, and protecting the health and safety of those consumers. The proposed Expert Committee on dietary supplements would develop state-level measures for

tracking serious adverse events associated with dietary supplements, increasing supplement-related information available to consumers, and reacting to developing scientific literature on dietary supplements. An accompanying DOH education campaign would give consumers and health care providers a broader understanding of the potential risks and benefits associated with dietary supplements, thus allowing New Yorkers to make well-informed choices about dietary supplements.

Notes

1 Institute of Medicine, *Complementary and Alternative Medicine in the United States* (2005), 258-259, website: *http://www.nap.edu/openbook/0309092701/html/258.html*, visited March 31, 2005.

2 Dietary Supplement Health and Education Act of 1994, Public Law No. 103-417 (October 25, 1994), codified throughout U. S. Code (2003), Title 21, Chapter 9, § 321 et seq.

3 Ibid.

4 Commission on Dietary Supplement Labels, Report of the Commission on Dietary Supplement Labels, November 1997, 12-13, website: *http://web.health.gov/dietsupp*, visited December 2, 2004.

5 U.S. Food and Drug Administration, Consumer Alert, "FDA Plans Regulation Prohibiting Sale of Ephedra-Containing Dietary Supplements and Advises Consumers to Stop Using These Products," December 30, 2003, *website: http://www.fda.gov/oc/initiatives/ephedra/december2003/advisory.html*, visited December 30, 2003.

6 *Nutraceutical Corp. v. Crawford*, No. 2:04 CV 409 TC, 2005 WL 852157 (D. Utah April 13, 2005).

7 "Governor Pataki Signs Law Banning Sale of Ephedra Products," November 3, 2003, website: *http://www.state.ny.us'governor/press/year03/nov3_03.html*; see also "Pataki signs ephedra ban," The Business Review, November 3, 2003, website: *http://albany.bizjournals.com/albany/stories/2003/11/03/daily7.html*, visited January 11, 2005; N.Y. Assembly Bill No. 6921, Ephedra Sale Ban, August 19, 2003.

8 U.S. Food and Drug Administration, "Instructions for Completing the MedWatch Form," website: http://www.fda.gov/medwatch/report/consumer/instruct.htm, visited January 11, 2005; see also U.S. Department of Health and Human Services, Office of Inspector General. Adverse Event Reporting for Dietary Supplements: An Inadequate Safety Valve, April, 2001.

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

10 U. S. Food and Drug Administration, News Release, "FDA News: Statement from FDA Deputy Commissioner Crawford regarding Metabolife," August 15, 2002, website: *http://www.fda.gov/bbs/topics/NEWS/2002/NEW00828.html*, visited October 18, 2002; P. J. Hilts, "U.S. in Criminal Inquiry on Metabolife Product," *The New York Times*, August 16, 2002, C1.

11 DHHS, OIG, Dietary Supplement Labels: An Assessment, ii-iii, 12-14; see also DHHS, OIG, Dietary Supplement Labels: Key Elements, 10-11 March 2003 (OEI-01-01-00120), website: *http://oig.hhs.gov/oei/reports/oei-01-01-00120.pdf*, visited December 7, 2004.

12 In concurrence with the recommendation of the Institute of Medicine, see Institute of Medicine, *Dietary Supplements: A Framework for Evaluating Safety*, (Washington, DC: National Academies Press 2005).

1. Ephedra: A Case Study in Dietary Supplement Safety

In February 2004, the U.S. Food and Drug Administration published a regulation prohibiting sales of dietary supplements containing ephedra, ten years after the agency first issued warnings about ephedra-based products. The effort to restrict ephedra has been surrounded by enormous controversy, pitting bereaved family members against advocates for consumer choice and industry representatives. In April 2005, one year after the FDA ephedra rule went into effect, a federal court stoked the fire by ruling in favor of a manufacturer's challenge to the regulatory ban.[1]

This chapter reviews a number of case histories that provide a sense of the emotional intensity of the debate over ephedra, and then examines the process that resulted in restricted ephedra sales. This process will provide a lens through which we can understand how dietary supplements are regulated, and will generate suggestions as to how the process can be improved, both on a national level and in New York State.

Case 1: A 23-year-old baseball player arrived at spring training, overweight and out of shape, to begin conditioning drills in the hot, humid Florida weather. He collapsed during a workout and was rushed to the hospital, where his body temperature reached 108 degrees. Doctors performed emergency treatment for heat stroke. Back at training camp, a bottle of an over-the-counter dietary supplement containing ephedra was found in his locker.[2]

The player, Baltimore Orioles pitcher Steve Bechler, died the next day, February 17, 2003. The official cause of death was multi-system organ failure preceded by heat stroke. According to the medical examiner, significant amounts of the dietary supplement containing ephedra contributed to Bechler's heat stroke. Also found in Bechler's blood were small amounts of two other stimulants, pseudoephedrine and caffeine.[3] Bechler's death was the most highly publicized adverse event associated with ephedra, but it was by no means the first.

Case 2: In 1998, Anne Marie Capati, a Huntington, NY, mother of two died after consuming an ephedra-based weight loss supplement under the written advice of her personal trainer. During a workout geared toward shedding her post-pregnancy weight, Capati collapsed and was rushed to the hospital. Later that night, after doctors determined that Capati had suffered a stroke, excessive and uncontrollable bleeding in her brain led to Capati's death. The doctors confirmed that the dietary supplement Capati was taking had elevated her blood pressure to a dangerous level, causing the stroke.[4]

Case 3: In 1996, 20-year-old Peter Schlendorf went to Florida with his friends for spring break. A resident of Asharoken, NY, he was a football player at the State University of New York at Albany. During the vacation, Schlendorf took an "herbal ecstasy" product purchased at a T-shirt shop. After Schlendorf took the pills, his heart "began to race uncontrollably."[5] His friends left him in the motel room, and when they came back, he was dead. An autopsy report concluded that Schlendorf had died from "cardiac arrhythmia caused by an herbal supplement containing the drug ephedra."[6] There was no other evidence of drugs or alcohol in Schlendorf's system at the time of his death.

The case reports of Bechler, Capati, and Schlendorf created significant media attention; their family members have played significant roles in the effort to ban ephedra.[7] These cases and others like them illustrate the intensity of the controversy generated by ephedra, and serve to draw attention to the scientific and regulatory issues surrounding dietary supplements.

* * *

Traditional Asian medicine practitioners have used ephedra to treat asthma, allergies, colds, and hay fever for more than 5,000 years. Ephedra is a natural source of the alkaloids ephedrine, pseudoephedrine, phenylpropanolamine (norephedrine), and cathine (norpseudoephedrine).[8] When chemically synthesized, ephedrine is regulated as a pharmaceutical-grade drug.[9] Many over-the-counter cold and flu remedies and prescription medications for bronchial asthma contain synthetic ephedrine.

Both controversial and lucrative, ephedra was most often used among American consumers for weight loss and to enhance athletic performance. Estimated sales of ephedra in 2003 reached approximately $1.4 billion.[10] Scientific data on the pharmacology of ephedra indicate that dietary supplements containing ephedrine alkaloids pose short- and long-term health risks.[11] One study found that the relative risk for adverse reactions among ephedra users is 10- to 40-fold higher than the risk among those who use herbal products generally.[12] Ephedra, especially when taken with caffeine,[13] increases such side effects as nausea, vomiting, psychiatric symptoms including anxiety and mood swings, and autonomic hyperactivity and palpitations; serious adverse events associated with ephedra and ephedrine have included deaths, heart attacks, cerebrovascular accidents, and seizures.[14]

The Long Road to Federal Ephedra Regulation

The Dietary Supplement Health and Education Act of 1994 (DSHEA)[15] curtailed the federal government's ability to regulate ephedra and other dietary supplements. Under DSHEA, no pre-market safety testing or approval of most dietary supplements is required and the Food and Drug Administration (FDA) is limited to post-market surveillance. Unlike prescription and over-the-counter drugs, the burden rests on the FDA to prove that a dietary supplement is unsafe, rather than on the manufacturer to prove that the product is safe. Further, the ability of the FDA to identify problems is limited, because DSHEA does not grant the FDA the authority to demand reports of dietary supplement-related adverse events from manufacturers.[16]

The FDA was concerned about ephedra and about the lax regulation of dietary supplements generally at the time of DSHEA's passage.[17] To lay the groundwork for regulation, the FDA "gathered and thoroughly reviewed a prodigious amount of evidence about epehdra's pharmacology,"[18] effectiveness and associated risk.

In 1994, the FDA began issuing medical bulletins and consumer alerts highlighting the dangers of ephedra-based dietary supplements and warning against individual brands that appeared to be especially hazardous.[19] When it was able to identify ephedra products that were adulterated with synthetic ephedrine, or were marketed as alternatives to illicit drugs, or were otherwise clearly unsafe, the FDA conducted enforcement actions against manufacturers. These included warning letters, court-authorized cease-and-desist orders, and seizure actions in the most urgent situations.[20] (See Appendix B.) In 1996, more than half the members of the FDA Food Advisory Committee could not identify a safe level for ephedrine alkaloids in dietary supplements and recommended that they be removed from the market.[21]

By June 1997, the FDA had received over 800 adverse event reports linked to ephedra—more than for any

other dietary supplement—related to products containing ephedra.[22] The increasing number of adverse event reports[23] and the FDA analysis of existing scientific literature led the FDA to conclude that ephedra supplements represented a significant public health threat.[24] The FDA published a proposed rule for ephedra-based supplements that would have set a recommended serving level and maximum daily dosage, would have required labels warning consumers not to use the product for more than seven days, and would have prohibited the combination of ephedra with other stimulant ingredients such as caffeine.[25] Supplement manufacturers responded with aggressive lobbying efforts against the proposed rule.[26]

In July 1999, the U.S. General Accounting Office (GAO) published a study critical of the proposed rule.[27] It recognized that the FDA lacked the authority to demand that manufacturers turn over their adverse event reports and therefore had to rely on voluntary reports.[28] The GAO also stated that the specific dosing and usage guidelines were insufficiently supported by evidence.[29] The FDA eventually withdrew the proposed rule.[30]

However, concern about ephedra did not cease. In 2001, the Marine Corps and the Navy restricted sales of ephedra-based products from base exchanges.[31] In 2002, in response to ephedra-associated deaths of young soldiers in training, the Army and Air Force removed all ephedra products from their on-base military stores.[32]

The National Institutes of Health Office of Dietary Supplements and the National Center for Complementary and Alternative Medicine sponsored an evidence-based review by RAND Corporation to assess the clinical efficacy and safety of products containing ephedra or ephedrine alkaloids.[33] A thorough review of the scientific literature and the evaluation of adverse event reports revealed five deaths, five myocardial infarctions, 11 cerebrovascular accidents, four seizures, and eight psychiatric diagnoses. The RAND researchers concluded that the use of ephedra is associated with doubled or tripled risk of psychiatric, autonomic, and upper gastrointestinal symptoms, as well as heart palpitations. The study found that the number of adverse events in young adults warranted further study of ephedra's physical effects, and that the use of ephedra in combination with caffeine was associated with numerous adverse events.[34] The study also found that, although ephedra may promote modest short-term weight loss in clinical trials, there were no data regarding long-term weight loss. Finally, RAND found that the evidence supporting the use of ephedra to enhance athletic performance was insufficient.[35]

In October 2002, U.S. Department of Health and Human Services Secretary Tommy Thompson asked the FDA to evaluate the available scientific evidence and recommend the strongest possible mandatory warning label for ephedra products.[36] Meanwhile, the American Medical Association, the American Heart Association, and numerous other professional health organizations urged the FDA to ban the sale of dietary supplements containing ephedra.[37]

In August 2002, at the request of the FDA, the U.S. Department of Justice began a criminal investigation to determine whether Metabolife International, Inc., manufacturer of the ephedra-based product Metabolife 356, had issued false statements to the FDA concerning adverse event reports. The FDA had unsuccessfully sought to obtain these reports from Metabolife International, Inc., even through litigation, since 1997.[38]

The GAO analyzed the Metabolife International, Inc. records in 2003 and found reports of 92 serious events (heart attack, stroke, seizure, or death) associated with Metabolife 356.[39] It noted that the types of events reported were consistent with the types of events reported to FDA, with the known physiological effects of ephedra, and with the RAND study.[40] The GAO also found that, where information on dosage or duration of use was included in the reports, most of the serious events "occurred among consumers who reported using the product within the guidelines on the Metabolife 356 label."[41]

By the end of 2003, the FDA had compiled scientific evidence it considered sufficient to conclude that ephedra presented an unreasonable health risk.[42] The FDA found "little evidence of ephedra's effectiveness except for short-term weight loss," and confirmed that ephedra raises blood pressure and stresses the circulatory system—reactions which have been "conclusively linked" to significant adverse events including heart ailments and strokes.[43]

On December 30, 2003, the FDA issued a consumer alert and letters to manufacturers of dietary supplements containing ephedrine alkaloids, indicating its intent to restrict sales of these products.[44] FDA based its regulatory actions upon the standard of "unreasonable risk," under which FDA's burden of proof "is met when a product's risks outweigh its benefits in light of the claims and directions for use in the product's labeling or, if the labeling is silent, under ordinary conditions of use."[45]

Almost ten years after the FDA issued its first warning about adverse events associated with ephedra,[46] the sale of dietary supplement products that contain ephedrine alkaloids was effectively banned nationwide as of April 12, 2004.[47] The FDA announced that "dietary supplements containing ephedrine alkaloids present an unreasonable risk of illness or injury when used according to product label instructions (or under conditions of ordinary use) and are therefore considered adulterated under Section 402(f)(1)(A) of the Federal Food, Drug, and Cosmetic Act."[48] The rule applied to all ephedra-containing dietary supplements, rather than to individual products or brands. The FDA announced that it could enforce the rule through a variety of actions including product seizures, injunctions, and criminal prosecution of violators.[49]

In the years between the 1997 proposed rule and the 2004 final rule, the FDA received numerous comments asserting the safety of ephedra as used in traditional Asian medicine.[50] The final regulation did not apply to ephedra used in most traditional Asian medicine preparations,[51] since these products are not regulated as dietary supplements under federal law.[52]

The ephedra regulation represented the FDA's first attempt to impose restrictions on the sale of a dietary supplement under DSHEA's regulatory framework.[53] Without prescribed authority to ban products, the rule articulated a legal standard by which FDA could take actions against dietary supplements under current regulatory restrictions.[54]

One year after the FDA's ephedra rule went into effect, a federal judge in Utah struck down at least part of the regulation. In *Nutraceutical Corporation v. Crawford*,[55] the U.S. District Court decided that the FDA had treated ephedra more like a drug or medical device than a dietary supplement; at least with respect to supplements containing low doses of ephedra, the FDA had exceeded its authority under DSHEA.

In formulating the ephedra regulation, the FDA had considered a risk-benefit analysis as a proper measure of DSHEA's "unreasonable risk" standard, and announced in the ephedra regulation: "In the absence of a sufficient benefit, the presence of even a relatively small risk of an important adverse health effect to a user may be unreasonable." But the *Nutraceutical* court felt this risk-benefit analysis "places a burden on the producers . . . to demonstrate a benefit as a precondition to sale, and that is contrary to Congress' intent [in DSHEA]."[56] In addition, the court found that the FDA had lumped together all ephedra supplements as posing an unreasonable risk of illness or injury under labeled or ordinary use, and that this broad restriction failed to give adequate consideration to low-dose ephedra supplements such as those sold by the plaintiff.

The court "remand[ed] to the FDA for further rulemaking" consistent with the ruling. The media widely reported that the FDA ban had been struck down. But despite some words from excited manufacturers at the

time of the Nutraceutical ruling,[57] it appeared likely at the time this report went to press (in May 2005) that FDA restrictions would remain in place against sales of dietary supplements containing more than 10 milligrams of ephedrine alkaloids.[58] At press time, it remains unclear whether any ephedra products will return to store shelves.[59]

* * *

Even before the FDA's ephedra restrictions were called into question, and with the ban on ephedra supplement sales in place, consumers continued to face dangers from other dietary supplements. The federal ephedra regulation increased the incentive for dietary supplement manufacturers to develop new ingredients and products, some of which may also pose significant risks. Restrictions on ephedra caused dietary supplement manufacturers to reformulate many of their weight-loss supplements; some new formulations include bitter orange, which contains synephrine.[60] The FDA is gathering data about the possible health impacts of a number of dietary supplements, including bitter orange, kava, usnic acid,[61] and aristolochic acid.[62]

Concern about the risk of dietary supplements other than ephedra exists in other nations as well. Due to the popularity of alternative medicines in Germany, the German Commission E was established as part of the Second Medicines Act in 1978. The Act required "scientific review of all medicines in the [German] pharmaceutical market, including conventional drugs, medicinal plants, and phytomedicines."[63] Commission E was responsible for evaluating botanical medicines. Manufacturers of botanicals provided the Commission with product quality information; the safety and effectiveness of 380 ingredients were determined by thorough review of scientific literature.[64] The Commission E monographs were first published in English in 1998, with an expanded version published in 2000.[65] Among other ingredients, the Commission did not approve Roman chamomile and yohimbe because of safety concerns.[66] Chaparral, comfrey, foxglove, and germander were classified as potentially unsafe.[67]

The Need for State Action

Barriers to effective federal regulation of dietary supplements led state and county regulators to act in advance of federal restrictions on the sale of ephedra-based dietary supplements. New York State, in particular, was a leader in protecting its citizens from the risks of ephedra. Westchester County banned sales of ephedra-containing dietary supplements to minors, and subsequently to all county residents.[68] In February 2003, the Suffolk County legislature enacted a ban on the sale to all consumers of dietary supplements containing ephedra; it was the first legislation of its kind in the country.[69] In the months that followed, Rockland County also banned sales of dietary supplements containing ephedra.[70] Effective October 2003, Governor George E. Pataki mandated a statewide ban on dietary supplements containing ephedra, citing concern for the health and well-being of New Yorkers.[71]

The April 2005 *Nutraceutical* case fixed a spotlight on the FDA's limited ability to regulate supplements. As discussed in chapter 4, the agency does not have the authority to require proof of safety before most dietary supplements are marketed or to demand adverse event reports after they are sold. Once a dietary supplement is on the market, the burden remains on the FDA to demonstrate that it poses an unreasonable health risk, rather than on the manufacturer to prove that it is safe. The overall regulatory picture suggests that the FDA may not be able to act swiftly and successfully to protect the public from other hazardous dietary supplements.

State-level action is necessary because of DSHEA's restrictions on federal oversight.[72] Some states have taken preliminary steps toward regulation by imposing warning labels on ephedra-based supplements,[73] or forbidding secondary school personnel from distributing dietary supplements to their students.[74] Prior to the FDA regulation, Illinois and California, in addition to New York, banned the retail sale of ephedra supplements. However, these state actions have occurred largely in response to a specific dietary supplement hazard and do not address systemic gaps in the regulation of dietary supplements.

DSHEA's limits on FDA are highlighted not only by the *Nutraceutical* decision, but also by the fact that it took FDA ten years to finalize a regulation before that court decision. Regardless of whether any ephedra regulation survives the *Nutraceutical* decision, the Task Force remains concerned that the system by which dietary supplements are regulated is flawed, and that there are insufficient mechanisms at the federal level for protecting consumers from those dietary supplements that are unsafe. Therefore, states must be prepared to address ongoing health risks and regulatory issues regarding dietary supplements where fedreal law does not preempt them from doing so. A well-designed system for assessing and responding to new data and risk information regarding dietary supplements with authority clearly assigned to state-level agencies is needed.

The Task Force strongly believes that the current regulatory structure for dietary supplements leaves New York consumers insufficiently protected. The remainder of this report presents the evidence for this conclusion and proposes solutions. Chapter 2 reviews the definition of dietary supplements and reports on the extent and reasons for their use. Chapter 3 describes the benefits and risks of dietary supplements and examines the data currently available in order to make these assessments. Chapter 4 covers the history of federal regulation of dietary supplements, while Chapter 5 addresses regulatory efforts made in New York, in other states, and by private organizations. Finally, Chapter 6 offers the Task Force recommendations for providing additional oversight of dietary supplements in New York State.

Notes

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16. See U. S. Code, Title 21, §§ 321(ff), 321(ff)(1), 342(f), 350b, 350b(c); "Statement of Lester M. Crawford, D.V.M., Ph.D., Deputy Commissioner, U.S. Food and Drug Administration, before the Subcommittee on Oversight of Government Management, Restructuring, and the District of Columbia, United States Senate," October 8, 2002, website: *http://www.FDA.gov/ola/2002/ephedra1008.html*, visited January 6, 2005.

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57. The president of one manufacturer reportedly responded to the ruling as follows: "I'm going to call my manufacturer and give him a new formulation. I'm going to give my label makers a call and order labels. I'm going to be back on the shelves [with ephedra] in five days." G. Warchol and R. Gehrke, "Ephedra ban lifted by judge in Utah," *The Salt Lake Tribune*, April 15, 2005, website: *http://www.sltrib.com/ci_2662440*, visited April 15, 2005.

58. An FDA spokesperson told the press that the "agency interprets the judge's language to mean that the ban remains in effect for products containing higher dosages of ephedra." Kimberly Rawlings quoted in P. Crabtree, "Ephedra ruling puzzles industry," *San Diego Union-Tribune*, April 16, 2005. An industry press release issued on the same day as the *Nutraceutical* decision predicted that the court's ruling "leaves in place a ban on all but those dietary supplements with 10 mg or less of ephedrine alkaloids per daily dose." Council for Responsible Nutrition, "CRN Responds to Utah Court Ruling on Ephedra," website: *http://www.crnusa.org/PR05_041405.html*, visited April 15, 2005.

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68. "N.Y. Legislature Bans Ephedra Supplements," *Associated Press*, June 3, 2003, website: *http://www.yourlawyer.com/practice/news.htm?story_id=6053&topic+Ephedra*, visited December 6, 2004. See also C. Bell, "Testimony of Consumers Union of US on Proposed New York State Ban on the Sale of Dietary Supplements Containing Ephedra Before the New York State Senate Committee on Consumer Protection," May 30, 2003, website: *http://www.consumersunion.org/food/ephedra-test503.htm*, visited December 6, 2004.

69. Laws of Suffolk County New York, Chapter 281, February 11, 2003, website: *http://www.Legislatorcooper.com/pressrelease_153.html*, visited July 20, 2004.

70. "Restrictions on the Sale of Dietary Supplements Containing Ephedra," Westchester County Law 863.901, website: *http://www.co.westchester.ny.us/consumer/Ephedra/ephedra.htm*, visited July 20, 2004. See also Local Law No. 8 of 2003, County of Rockland, State of New York, website: *http://www.co.rockland.ny.us/Legislature/Local/law_8_2003.pdf*, visited July 20, 2004.

71. "Governor Pataki Signs Law Banning Sale of Ephedra Products," November 3, 2003, website: *http://www.state.ny.us/governor/press/year03/nov3_03.htm*, visited July 22, 2004. See also "Pataki Signs Ephedra Ban," *The Business Review*, November 3, 2003, website: *http://albany.bizjournals.com/albany/stories/2003/11/03/daily7.html*; visited March 31, 2005; NY Assembly Bill No. 6921, August 19, 2003.

72. "States Urged To Lead Dietary Supplement Enforcement," *Food Labeling and Nutrition News* 3(1995):103. The regulatory authority of states is discussed in Chapter 5.

73. See, e.g., additional labeling requirements on ephedra products in Texas Administrative Code (2002), Title 25, Part 1, Chapter 229, § 229.463.

74. See Michigan Compiled Laws, § 380.1317 (1)(a), (1)(b). Exceptions are provided for employees providing otherwise legal supplements to their own children, or providing supplements to students in activities entirely unrelated to school (and with whom the employee has no in-school contacts). Michigan Compiled Laws, § 380.1317 (2)(a), (2)(b).

2. Consumer Choice: Dietary Supplement Utilization

A dietary supplement is defined as an ingested product, intended to supplement the diet, which bears or contains one or more of the following dietary ingredients:

- a vitamin;
- a mineral;
- an herb or other botanical;
- an amino acid;
- a dietary substance for use by man to supplement the diet by increasing total dietary intake; or
- a concentrate, metabolite, constituent, extract, or combination of any ingredient described above.

Source: United States Code (2003), Title 21, § 321 (ff)

The Dietary Supplement Health and Education Act of 1994 (DSHEA) defines dietary supplements as products, not drugs, that are taken by mouth and contain an ingredient intended to supplement the diet.[1] The dietary ingredient can be a vitamin, mineral, herb, amino acid, a substance used to increase total dietary intake (e.g., an enzyme), concentrate, metabolite, constituent, or extract. The ingredient can stand alone or be compounded to create a desired therapeutic effect. This definition is substantially broader than previous legal and commonly used definitions.[2] Dietary supplements are produced in a variety of forms including teas, powders, tablets, capsules, tinctures, and oils.

Vitamins are organic compounds that cannot be synthesized by the body, but are necessary for its proper functioning. Vitamins A, D, E, and K are fat-soluble[3] and can be stored for the body's future use. Water soluble vitamins, including vitamins B and C,[4] cannot be stored by the body and therefore need to be replenished through diet in order to avoid deficiencies. Vitamin deficiencies can interfere with metabolic processes and cause severe illness. For example, pellagra is the result of niacin (vitamin B3) deficiency; scurvy is the result of ascorbic acid (vitamin C) deficiency; beriberi is the result of thiamin (vitamin B1) deficiency; and rickets can result from vitamin D deficiency.

Minerals are inorganic elements and salts extracted from the earth. The human body requires a substantial amount of the major minerals—calcium, chloride, magnesium, phosphorus, potassium, sodium, and sulfur—for healthy survival. The trace minerals—chromium, copper, fluoride, iodine, iron, manganese, molybdenum, selenium, and zinc—are needed in much smaller amounts. Like vitamins, minerals need to be acquired in the diet to avoid deficiencies such as anemia, which can result from insufficient iron intake.

Botanicals are referred to in a number of different ways, including herbal remedies, phytomedicines, and phytopharmaceuticals.[5] An herbal remedy is a plant or plant part (root, flower, leaf, fruit) that is used for its medicinal or therapeutic properties.[6] The potency of herbal products can vary depending on each plant's growing conditions, level of maturity when harvested, and the processes used to dry and store each ingredient.[7] Historically, approximately 2,500 different herbs have been used for medicinal purposes.[8]

Other dietary supplement ingredients include amino acids, metabolites, and extracts. Amino acids are the constituents of proteins. Amino acids can be categorized into three groups: indispensable (essential), conditionally indispensable, and dispensable (non-essential). Indispensable amino acids must be consumed in the diet.[9] Conditionally indispensable amino acids[10] can be synthesized by the human body under most conditions, but may require dietary supplementation under certain pathophysiological conditions, such as catabolic stress or neonatal prematurity.[11] Five amino acids are dispensable,[12] meaning that they can be synthesized from other amino acids or complex metabolites. Metabolites are substances that are produced by metabolic action or are necessary for a metabolic process. An extract is a substance, usually a biologically active ingredient of plant or animal tissue, prepared by the use of solvents or evaporation to separate the substance from the original material.

Prevalence

Note: Inclusion in the following discussion does not constitute endorsement of particular dietary supplement products or dietary supplement ingredients.

An estimated 29,000 varieties of dietary supplements are on the market with 1,000 new products being introduced each year.[13] Dietary supplements are sold in a variety of retail establishments. Because they are not considered drugs under federal or New York State law, no prescription is required to purchase or dispense dietary supplements in New York, and they can be sold in health clubs, supermarkets, pharmacies, health food stores, and other retail establishments. As part of their practice, traditional Asian medicine and complementary and alternative medicine (CAM) providers may dispense supplements.

Thousands of dietary supplements are also available for purchase via the Internet. The online purchase of dietary supplements is particularly attractive to minors. A 2004 report estimated that 18 million children between the ages of 12-17 years have used the Internet.[14] Data from 2001 indicate that approximately 25 percent of teenagers using the Internet have searched for information about diet, exercise and general health.[15] The same study revealed that approximately 14 percent of these teenagers lied about their age in order to access age-restricted web sites. The ability to bypass age-related safeguards and access products that are not intended for use by children is disconcerting and potentially dangerous.

More than 100 million Americans use dietary supplements,[16] spending $18.7 billion on them in 2002.[17] Data on the consumption of dietary supplements vary widely. Inconsistent research indicates that as few as 3 percent and as many as 97 percent of Americans take dietary supplements on a regular basis.[18] Other studies estimate that at least 30 percent of Americans use vitamin and mineral supplements regularly[19] and approximately 33 percent use at least one nonvitamin and/or nonmineral supplement regularly.[20] Among cancer patients, the use of "unconventional"[21] medicines, including herbal therapies, has been reported to be as low as 5 percent[22] and as high as 60 percent.[23]

Excluding industry surveys that are generally used for tracking and marketing purposes, national survey data do not provide a clearer estimate of the number of dietary supplement consumers. The National Health and Nutrition Examination Survey (NHANES)[24] is a data collection system within the National Nutritional Monitoring and Related Research Program.[25] It provides the best available data regarding individual consumption of foods and beverages in the United States. Historically, it placed little emphasis on the use of dietary supplements.[26] However, the 1999-2004 survey (which at press time has not been released) included questions regarding the use of dietary supplements and laboratory tests for vitamins A, B6, B12, C, and D, selenium and eight different phytoestrogens.[27]

In 1999, the U.S. Centers for Disease Control and Prevention (CDC) reported on the estimated prevalence of dietary supplement use within the American population; results were stratified by various demographic and descriptive characteristics.[28] The study incorporated data from NHANES and the Hispanic Health and Nutrition Examination Survey for the years 1988-1994. The survey did not specifically question use of herbs, amino acids, metabolites, or other biologic extracts; therefore, the prevalence of dietary supplement use may be underestimated.[29] The report found that approximately 40 percent of the U.S. population use dietary supplements. Women are more likely than men to use dietary supplements and non-Hispanic whites are more likely to take dietary supplements than non-Hispanic blacks and Mexican Americans.[30] Several other studies also emphasize the high prevalence of dietary supplement use by women,[31,32,33] and non-Hispanic whites.[34,35,36]

Based on data from 2002, the CDC released a report that provided a more comprehensive review of dietary supplement use in the United States. The report included a descriptive chart on the use of nonvitamin, nonmineral natural products and listed echinacea, ginseng, ginkgo, garlic, and glucosamine as the five most frequently used dietary supplements.[37]

Rationale for Use

Members of certain ethnic groups may rely on herbal remedies, that are available in the United States as dietary supplements, as part of their cultural tradition.[38,39,40,41,42] For example, "[herbal medicine] has been an integral part of Chinese culture and medical practice for nearly 1600 years."[43] Many Hispanics also integrate herbal medicines with their reliance on conventional medical practitioners.[44] In one study, Hispanics were more likely to grow their own herbs and more likely to obtain information on herbal use from a family member, suggesting that use of herbs is more integrated into cultural practices in this group than in non-Hispanic whites.[45] Additionally, some Indian populations practice Ayurveda, a traditional medicine system[46] with a "a rich tradition in plant pharmacotherapy."[47]

Consumers also use dietary supplements in their attempts to ensure general health and nutrition, improve athletic performance, enhance personal appearance, and to avoid the harmful or unpleasant side effects associated with pharmaceuticals and other forms of conventional medical treatment.[48,49] Herbal remedies, in particular, are taken for reasons other than nutrition.[50] Some consumers will use supplements to treat benign self-limited conditions (e.g., echinacea for the common cold), while others will use them in an attempt to manage the symptoms of serious and/or chronic illnesses (e.g., saw palmetto for benign prostatic hyperplasia or glucosamine for arthritis).

Ensuring Health and Wellness

American consumers often cite health promotion as a reason for using dietary supplements.[51] In an effort to ward off infection, treat and prevent age-related eye diseases, including macular degeneration and cataracts, and to abate chronic ailments such as cardiovascular disease, diabetes, and cancer, many people use antioxidants including vitamins A, C, and E, and the mineral selenium.[52] By neutralizing free radicals, antioxidants, whether consumed individually or in a multivitamin compound, are thought to prevent cell damage.[53] Specifically, antioxidants are promoted to inhibit oxidation (which can exacerbate degenerative diseases)[54] thus potentially reducing risk and alleviating symptoms of diseases such as Alzheimer's and Parkinson's.

Allicin, the chemical that gives garlic its distinctive odor and flavor, is also marketed as a medicinally active ingredient that promotes health and wellness. Crushed garlic bulb, oil, powder, and tablet supplements are used to lower blood pressure,[55] to reduce cholesterol in an effort to abate cardiovascular risk,[56] and to prevent atherosclerosis.[57] In Europe, garlic is approved as primary prevention of atherosclerosis and as an adjuvant treatment for high cholesterol.[58]

Ginkgo biloba is another commonly used dietary supplement in the United States[59] that is approved as a medicine in Europe.[60] In Germany, ginkgo is used to treat cerebral circulatory disturbances, reduced functional capacity, vertigo, and tinnitus.[61] Germany has also approved ginkgo as a treatment for Alzheimer's disease based on claims of its ability to enhance memory. Americans use ginkgo biloba for a host of ailments including dementia, intermittent claudication, and macular degeneration.

Improving Athletic Performance

The use of "sports supplements," including branch amino acids, choline, glutamine, l-carnitine, and whey protein, is very common at all levels of athletic competition.[62] Athletes often use these supplements in an attempt to meet or exceed the nutritional demands of organized sports or competitive bodybuilding. Androstenedione (andro)[63] was once consumed as a dietary supplement until it was placed on the federal list of controlled substances along with other steroids and precursor compounds under the Anabolic Steroid Control Act of 2004. Among the more popular sports supplements still available are creatine and dehydroepiandrosterone (DHEA).

Creatine is a non-protein combination of three amino acids produced in the liver, kidneys, and pancreas to generate and release energy. Because creatine generates brief surges of energy and acts as a catalyst for muscle contractions, athletes believe it can enhance athletic performance.[64] Common preparations include tablets and caplets, a powder that can be mixed with juice or water, and a concentrated solution. Creatine is also a common ingredient in energy bars and sports drinks.

The FDA banned DHEA in the early 1980s, but as a result of DSHEA, it was reclassified as a dietary supplement in 1994. Once inside the body, DHEA is metabolized into other androgenic substances including androstenediol, androstenedione, and the steroid hormones estrogen and testosterone. Although not supported by evidence,[65] DHEA manufacturers claim the supplements boost immunity, treat fatigue, strengthen bones, build muscle mass, reduce fat, and reduce injury recovery time. The supplements are available in capsules, chewing gum, or drops that are placed under the tongue. DHEA was specifically excluded from the 2004 Anabolic Steroid Control Act.[66]

Some products purported to be "sports supplements" do not meet the DSHEA definition for dietary supple-

ments. One example is the synthetic steroid tetrahydrogestrinone (THG), which gained notoriety in 2003 when the United States Anti-Doping Agency (USADA) announced that a track-and-field coach had reported that U.S. and international athletes were using an undetectable steroid. The USADA received a syringe containing the substance, and forwarded it to a laboratory at the University of California at Los Angeles.[67] Chemical testing of the contents of the syringe revealed THG, whose chemical structure resembles that of other banned steroids.[68]

Shortly after, the FDA disputed THG's status as a dietary supplement. The FDA announced that "purveyors of THG may represent it as a dietary supplement, [but] in fact it does not meet the dietary supplement definition" and is instead a "purely synthetic 'designer' steroid derived by simple chemical modification, from another [USADA-banned] anabolic steroid."[69] The FDA also announced that it considered THG to be an "unapproved new drug that cannot be legally marketed without meeting the agency's approval standards," that it had "little knowledge of THG's safety," and that "its structure and relationship to better known products leads the FDA to believe that its use may pose considerable health risks."[70]

THG is now banned by the World Anti-Doping Agency (WADA), whose list of prohibited substances is used by the USADA and the International Olympic Committee.[71]

THG was included among the steroid precursor compounds added to the federal list of controlled substances under the Anabolic Steroid Control Act of 2004.

Enhancing Personal Appearance

Modern high-fat, high-calorie diets combined with physical inactivity have contributed to the epidemic of overweight and obesity in America. Based on 1999-2002 national data, approximately 65 percent of U.S. adults are either overweight or obese.[72] In 2002, 57 percent of New York State adults were overweight or obese.[73]

Evidence indicates that higher levels of body weight and body fat are associated with an increased risk for the development of numerous adverse health consequences, including heart disease, diabetes, hypertension, osteoarthritis, sleep apnea, psychiatric disorders (mainly depression and anxiety), and stroke.[74] Seeking to avoid these ill health effects and to enhance their personal appearance, Americans spend $30 billion per year on weight loss aids including dietary supplements.[75]

Prior to the federal regulation of ephedra in April 2004, it was estimated that approximately 2 million adults took ephedra-containing weight loss products daily.[76] In anticipation of the regulation, many manufacturers created "ephedra-free" supplements that are promoted to enhance weight loss without harmful side effects. The most popular "replacement" ingredient in these products is citrus aurantium, also called bitter orange. Many major manufacturers of ephedra-containing products, including New York-based firms,[77] now sell weight loss products that include bitter orange.[78] However, bitter orange contains synephrine, which, like the ephedrine alkaloids, increases blood pressure and increases the risk of cardiovascular events.[79] In addition, bitter orange contains compounds that inhibit metabolic processes and can increase the blood levels of many drugs.[80]

Chitin/chitosan and chromium are also common ingredients in dietary supplement weight loss products. Chitin is a dietary fiber derived from the shells of crab, shrimp, and lobster. Chitin molecules have the ability to latch on to heavy metals, amino acids, and fat through chelation.[81] This may enable chitin to capture fat before the body is able to absorb it. Chitosan is a synthetic version of chitin, that is also promoted and consumed for

body weight reduction.[82,83] Chromium is an essential trace mineral required for sugar metabolism.[84] Reported effects include increases in basal metabolic rate and lean body mass and a decrease in body fat percentage.[85] The most popular formulation, chromium picolinate, is marketed as a "fat burner" and is available in pills, chewing gum, sports drinks, and nutrition bars.[86]

Avoiding Pharmaceuticals

The use of dietary supplements is common among people with chronic and/or recurrent conditions[87] including arthritis, chronic back pain, or other musculoskeletal pain.[88] Osteoarthritis is the most common form of arthritis in America and is the leading cause of pain and disability, including lost time from work.[89] An estimated 21 million Americans suffer from osteoarthritis, a number expected to grow due to the aging of the population and high rate of obesity.[90]

Osteoarthritis sufferers often take dietary supplements in combination with or instead of prescription anti-inflammatory medications. Patients use dietary supplements hoping to relieve pain while avoiding the gastrointestinal side effects common to nonsteroidal anti-inflammatory drugs (NSAIDs). The most commonly used "anti-arthritic" supplements are chondroitin and glucosamine. Consumers can take either supplement as a stand-alone therapy, but most often use a combination product. According to Information Resources Inc.,[91] total glucosamine and chondroitin sales were $274 million between January 5, 2002 and January 5, 2003.[92]

Chondroitin is a naturally occurring compound found in mammalian cartilage, [93] bone, cornea, skin, and the arterial wall. It promotes and maintains the structure and function of cartilage. It is marketed to offer pain relief of osteoarthritic joints and to have anti-inflammatory properties.[94] Glucosamine is essential for the construction of glycosaminoglycans (GAGs) in articular cartilage; reduced GAG content corresponds with the severity of osteoarthritis.[95] Therefore supplementation may be beneficial.

* * *

Several factors contribute to the increasing consumption of dietary supplements in America.[96] Consumers are drawn to dietary supplements because of their nonprescription status, direct-to-consumer advertising, and the perception that natural products are inherently safe.[97] Additionally, widespread media attention to dietary supplements sends the public the message that they can self-medicate for many conditions.[98] Unfortunately, most Americans have misconceptions about the regulation of dietary supplements, believing that supplements must be approved by a government agency, that manufacturers can make claims about safety and effectiveness only if there is solid scientific evidence to support them, and that warnings about potential side effects or dangers are required.[99]

On its consumer website, the National Center for Complementary and Alternative Medicine advises those seeking information on dietary supplements to speak to their health care provider, consult a dietitian or pharmacist, or to conduct their own research on the supplement they are interested in.[100] This advice is also endorsed on the FDA website.[101] In theory, it is good advice. However, in practice, some physicians receive only limited training in clinical nutrition[102] or complementary and alternative medicine.[103] And, the majority of dietitians perceive themselves as having little or no knowledge regarding herbal supplements.[104] Therefore, conventional medicine practitioners may lack the information necessary to effectively discuss the use of dietary supplements with their patients. There is also widespread skepticism about the proliferation of complementary and alternative medicine practices among conventionally trained practitioners, with deficiencies of evidence as the predominant reason cited.[105,106,107,108]

Additionally, consumers may not be adequately or accurately researching the dietary supplements they are considering using. Searches for health information are one of the most common reasons that consumers use the Internet; specifically, "80 percent of American Internet users have searched for information on at least one major health topic online."[109] Unfortunately, evidence indicates that most consumers never check "About Us" sections of websites, never try to identify the authors or owners of the site, and never read disclaimers or disclosure statements when they are available.[110] These oversights are especially risky for current and prospective dietary supplement consumers because the quality of website information varies and many sites are affiliated with manufacturers or paired with online order catalogs.[111] In addition, the Federal Trade Commission has taken legal action against a number of websites that contain incorrect and deceptive information.[112]

* * *

In summary, as defined by DSHEA, dietary supplements may be vitamins, minerals, amino acids, botanicals, metabolites, or extracts. Using dietary supplements for health and wellness, improving athletic performance, enhancing personal appearance, and as a substitute for pharmaceuticals, most consumers are misinformed about the regulation, safety, and effectiveness of dietary supplements. Dependent on the limited training of physicians on CAM and clinical nutrition, along with unreliable Internet information, most consumers have misconceptions about the risks associated with dietary supplement use. As discussed in Chapter 3, these misconceptions may have dangerous consequences.

Notes

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3. Safety: The Benefits and Risks of Dietary Supplements

Recognizing that the word "natural" is not synonymous with, or necessarily correlated with, the word "safe" is important when considering dietary supplement use. Although established pharmaceutical and nutrition companies manufacture some dietary supplements, the industry is largely unregulated and nonstandardized. Some critics believe that there exist manufacturers that comprise "a significant section of the industry that is willing to take advantage of the unregulated environment and take chances with public health in order to make [money]."[1]

Further, credible scientific knowledge about the efficacy and safety of many readily available dietary supplements is inadequate. Because there is no regulatory requirement for dietary supplement manufacturers to perform pre-market clinical studies, formal research on the safety and efficacy of dietary supplements is uncommon.

Some manufacturers and consumers mistakenly consider historical use as a proxy measure of the safety and efficacy of dietary supplements, especially for herbal remedies that have been used for hundreds of years. However, reliance on historical use as a measure of safety is problematic for several reasons. First, herbal treatments vary widely in the concentration of active ingredients from one preparation to another; assumptions about safety based on one preparation may not apply to another. For example, the discovery of wide fluctuations in potency and risk helped determine the safe use of foxglove for digitalis preparations.[2]

Second, side effects that develop slowly may be especially difficult for practitioners to link causally to particular herbal remedies, especially when multiple herbs are used over time or in a single preparation. For instance, the severe liver damage that can result from kava use may develop over many months.[3]

Third, while traditional healers may have extensive knowledge about which parts of plants to use in which ways, and when and where to harvest them,[4] this knowledge may be lost in the transition of a remedy from traditional settings to the modern context; for example different plants or parts of plants may be substituted with dangerous effects. In one noted case, Belgian physicians decided to add a plant named han fang ji (stephania tetrandra) to their clients' regimens. However, their suppliers substituted a plant named guang fang ji (aristolochia fangchi), resulting in more than 100 cases of renal failure, requiring dialysis and/or kidney transplant.[5]

Fourth, patterns of current use may differ greatly from traditional use. For instance, ephedra was traditionally used for short-term symptom management, such as nasal congestion associated with colds and the flu. Contemporary practice has included longer-term use, for instance as a tool for weight loss, and therefore may carry greater risks.[6]

Finally, genetic differences may explain the ability of one group to tolerate a particular substance, though it may pose greater risks to another group or to the general population. Risks associated with alcohol, for instance, are varied for different genetic sub-groups of the population.[7] Similarly, genetic differences in the liver's ability to metabolize kava may increase its toxicity for some consumers.[8]

Not all dietary supplements can claim a long history of use, and for these products even less may be known about safety. Many dietary supplements have been developed in recent years. Evidence of the safety and efficacy of products now on the market is inadequate and not likely to improve under current regulations.[9]

Evidence

The existing literature on many complementary and alternative medicine (CAM) practices, including dietary supplement use, is of highly variable quality.[10,11,12] For the purpose of this report, primary evidence includes only original research with valid data collection that results in peer-reviewed published articles. Secondary evidence includes review articles, compilations, and opinion pieces based on primary evidence. Although a substantial amount of secondary evidence on the use, safety, and efficacy of dietary supplements is available, there is a dearth of primary evidence. Among the obstacles to obtaining useful primary evidence on dietary supplements are poorly designed trials, difficulty retrieving quality literature, and the impracticability of using an evidence-based approach to evaluate available studies.[13]

Primary Evidence

There are several limitations and methodological flaws in the available literature including insufficient statistical power, sampling errors, absence of control groups, and incomplete reporting.[14,15,16,17] A review of almost 3,000 clinical trials of Traditional Chinese Medicine (TCM) found major methodological flaws in most studies.[18] Specifically, the method of randomization was often insufficiently described, blinding was rarely used, and only a few studies had adequate sample sizes. Further, effectiveness was rarely quantified or reported, and over half the studies did not report data on baseline characteristics or on side effects. However, most trials claimed that the tested treatments were effective, indicating that publication bias may be common.[19]

Many studies on dietary supplements are designed to assess beneficial effects and thus do not provide complete safety information.[20] And, although there is agreement that dietary supplements should be evaluated in light of present knowledge of pharmaceutical sciences and medicinal chemistry,[21] there is a widespread lack of interest in herb-drug interactions within the pharmaceutical and herbal industries.[22] The lack of research can also be ascribed to limited funding for clinical trials.[23]

Secondary Evidence

Several sources of secondary evidence are available for evaluating dietary supplements.[24] Unfortunately, systematic reviews and meta-analyses provide little information on the safety of dietary supplement products aside from repeating the adverse events recorded in primary research.[25]

Among the leading sources of information are the International Bibliographic Information on Dietary Supplements (IBIDS) database, the Cochrane Library, and the Natural Medicines Comprehensive Database. IBIDS is compiled by the Office of Dietary Supplements at the National Institutes of Health and offers access to citations and abstracts from international scientific literature.[26] The Cochrane Library is a collection of evidence-based medicine databases that includes the Cochrane Database of Systematic Reviews.[27] Cochrane reviews are considered to be extremely rigorous and they have been favorably compared with systematic reviews published

in medical journals.[28] Reviews on dietary supplements such as kava, glucosamine, and garlic are included in the Cochrane Library. The Natural Medicine Comprehensive Database contains over 1,000 monographs detailing the potential safety and efficacy of individual dietary supplements.[29]

Additionally, the Physicians' Desk Reference (PDR) organization has published the PDR for Herbal Medicines (First edition 1998, Second edition 2000), the PDR for Nutritional Supplements (First edition 2001), and the PDR for Nonprescription Drugs and Dietary Supplements (2004). These reference books include information on the indications, usage, and risks associated with many commonly used dietary supplements.

In 2005, at the request of the Food and Drug Administration (FDA), the Institute of Medicine (IOM) published a framework for assessing dietary supplement safety.[30] The framework includes a process for critically reviewing available scientific evidence and properly evaluating the benefits and/or risks of particular supplements.

Guiding Principles for Evaluating Dietary Supplement Risk:

- Absence of evidence of risk does not indicate absence of risk.
- Proof of causality or proof of harm is not necessary to determine risk.
- Integration of data across different categories of information and types of study design can enhance biological plausibility and identify consistencies, leading to conclusions regarding level of risk.

Adapted from: Institute of Medicine, Dietary Supplements: A Framework for Evaluating Safety (Washington, DC: National Academy Press, 2005)

Potential Benefits

A number of dietary supplements have beneficial health effects that are substantiated by scientific evidence. For example, researchers agree that during the first weeks of pregnancy, folic acid in higher doses than typically consumed by diet alone has beneficial fetal health effects.[31] Therefore, to prevent neural tube defects including spina bifida, the U.S. Public Health Service recommends 400 micrograms of supplemental folic acid daily for all women of childbearing age.[32] The New York State Department of Health advises all women, including young girls, to either consume a 400 microgram supplement or eat fortified food daily.[33] Since January 1, 1998, all flour and uncooked cereal grains in the United States have been supplemented with 140 micrograms of folate per 100 grams of flour.[34]

For people that do not consume a variety of foods, selected dietary supplements, including vitamins and minerals, can be taken to ensure adequate consumption of required nutrients. For example, physicians may recommend supplements for elderly patients that are fatigued due to low iron levels.[35] Also, because vitamin D deficiency is common among older people, experts recommend that all older adults routinely take vitamin D supplements.[36]

It is important to note that some, but not all dietary supplement use correlates to deficient dietary intakes.[37] As discussed in Chapter 2, consumers use dietary supplements for a variety of reasons ranging from weight loss to pain management. Information on the benefits and risks of these supplements is often unavailable or incon-

clusive. The lack of evidence of harm does not necessarily indicate that a dietary supplement is safe but rather that there is no evidence to the contrary.[38]

An example of a dietary supplement for which there is no known evidence of harm is saw palmetto.[39] Saw palmetto is the most commonly used herbal supplement for the treatment of symptomatic benign prostatic hyperplasia (BPH).[40] BPH is the non-cancerous overgrowth of the prostate that affects up to one-third of men in the fifth decade of life and about half of men in the seventh decade of life.[41] Treatment options for BPH include medication, surgery, and dietary supplements. Prescription drugs provide some relief for some patients but are associated with the risk of diminished sex drive. Because nerves surround the prostate, surgical procedures are associated with increased risk of impotence and incontinence.[42] Saw palmetto supplements are effective in reducing the difficulties associated with prostate enlargement,[43] including urinary flow[44,45,46] and excessive nighttime urination,[47,48] but they do not reduce glandular enlargement.

Other dietary supplements are known to have side effects that are comparable to those posed by non-prescription and over-the-counter drugs. A variety of dietary supplements fall into this category including phytoestrogens that are used to prevent and treat the symptoms of menopause.

In 2002, the Women's Health Initiative, an eight-year study of the effects of hormone replacement therapy (HRT) in menopausal women, was halted after five years because researchers detected an increased risk of breast cancer and coronary heart disease among the participants taking a combination of estrogen and progestin. The American Medical Association advised its members of alternatives to offer their patients including phytoestrogens.[49]

Phytoestrogens are plant compounds that act similarly to human estrogen, though they are generally less potent and have fewer and less severe side effects. The three classes of phytoestrogens are isoflavones, coumestans, and lignans. High concentrations of each are found in legumes such as soybeans and chickpeas. Additionally, several pharmaceutical companies manufacture and/or distribute phytoestrogen-based products to supplement the diet.[50]

One such product is red clover, which contains the isoflavones genistein, daidzen, biochanin A, and formononetin. Genistein has the greatest bioactivity of all of the isoflavones.[51] Red clover has therefore been used to reduce menopausal symptoms, including hot flashes, night sweats, vaginal dryness, and mood swings. It may also aid in the maintenance of bone density in the lower spine of menopausal and perimenopausal women,[52] and has been associated with a significant increase in the cortical bone of the radius and ulna.[53]

The phytoestrogen black cohosh may be an effective treatment for some symptoms of menopause including palpitations and hot flashes.[54] Therefore, the American College of Obstetricians and Gynecologists added black cohosh to its published clinical practice guidelines for the short-term (six months or less) treatment of vasomotor symptoms.[55] Black cohosh is approved in Germany as a treatment for dysmenorrhea, premenstrual discomfort, and other menopausal symptoms including irritability, nervousness, sleep disturbances, vertigo, sweating, tinnitus, and depression.[56]

Black cohosh interacts with hormones to produce an estrogen-like effect, which may decrease certain menopausal symptoms including hot flashes, night sweats, and psychological disturbances.[57,58] In 2000 black cohosh generated $6 million in U.S. sales.[59]

Black cohosh preparations have shown a low incidence of adverse side effects, which have included stomach discomfort, headache,[60] heaviness of the legs, and weight changes.[61] Long-term safety data on black cohosh are not available.

Potential Risks

The FDA does not evaluate the safety, efficacy or quality of dietary supplement ingredients or products. Therefore, consumers, who often assume that "natural" is synonymous with "safe" may be taking dietary supplements at their own risk. Mega-dosing, delaying conventional medical treatment, the concomitant use of supplements and pharmaceuticals, and contraindicated use are potential risks associated with popular dietary supplements. And, because dietary supplements are not subject to standardized quality control measures, contamination, adulteration, and dosage inconsistency are common. Another potential risk is the increasing use of dietary supplements by children. Additionally, there are other dietary supplement ingredients and products that for various reasons, including their inherent toxicity, should be considered unsafe.

Mega-dosing

A concern with all dietary supplements, even those that are not known to be harmful, is the consumer misperception that "if a little is a good, more has to be better."[62] This mega-dosing of even "safe" dietary supplements can cause toxic effects. Adverse effects of consuming excessive calcium may include high blood calcium levels, kidney stone formation and kidney complications.[63] Chronic and acute hypervitaminosis A, or vitamin A overdose, can be poisonous. Chronic hypervitaminosis A can lead to bone and skin alterations, can cause liver abnormalities, and can have adverse effects on the central nervous system.[64] Symptoms of acute hypervitaminosis A include nausea, vomiting, headache, increased cerebrospinal fluid pressure, vertigo, blurred vision, and lack of muscular coordination.[65] Excessive vitamin D intake has been linked to hypercalcemia.[66]

Delay of Care

Some dietary supplement use bears the risk of delaying necessary and effective conventional medical treatment. For many people this delay may exacerbate their disease. For instance, sexually transmitted diseases such as the human papilloma virus (HPV) and herpes simplex virus II require treatment by a physician. Although visible manifestations of these diseases may dissipate, significant internal complications may remain, and must be treated. For instance, certain strains of HPV are linked to cervical and vulvar cancer.[67] Herpes is associated with cervical cancer and encephalitis.[68] Herpes infection of pregnant women can lead to neonatal infection, causing meningitis and other serious complications, including death.[69]

The dietary supplement beta-mannan, an aloe-based pill, has been marketed as a treatment for both herpes and HPV.[70] Clinical trials are inconclusive regarding the efficacy of oral or topical aloe vera for herpes.[71] Fix-It Oral Antiviral is another dietary supplement that claims to heal and suppress herpes outbreaks.[72] Fix-It supplements contain over 20 ingredients including dextran sulfate, pentosane polysulfate, chondroitin sulfate, heparin sulfate, glucosamine 6-sulfate, echinacea, and elderberries.[73] None of these ingredients is part of the standard treatment of these diseases.[74] Because of the stigma associated with sexually transmitted diseases, those infected may be particularly susceptible to promises about treatments that do not require a doctor's visit. However, time spent using ineffective treatment increases the potential risk to this group, to their sexual partners, and to the offspring of infected women.

Concomitant Use

Millions of people (an estimated 18.4 percent of prescription drug users[75,76]) take conventional medications concurrently with herbal supplements or high dose vitamins.[77] Specifically, one in six patients taking prescription drugs also takes one or more herbal or other dietary supplement.[78] As described in further detail in Appendix A, dietary supplements can interact with a number of common prescription and over-the-counter medications.

Interactions between dietary supplements and pharmaceutical drugs can be classified as either pharmacokinetic or pharmacodynamic. Pharmacokinetic interactions interfere with the absorption, metabolism, or excretion of drugs; pharmacodynamic interactions alter the pharmacological activity of drugs.[79] The risk of interactions is especially high among the elderly because older people take more medications than younger people do[80] and because adults over age 60 are the most likely to take more than one dietary supplement.[81]

Examples of supplements that interact with drugs include valerian, which should not be used concomitantly with barbiturates because of the risk of excessive sedation, and ginseng, which may affect blood glucose levels and should be avoided by patients with diabetes mellitus.[82] The concomitant use of St. John's wort or calcium with prescription medications can also cause significant harm.

Hypericin, the active ingredient in St. John's wort, is a prescription medicine in Germany[83] that is used for the treatment of depression and anxiety. Its alleged antidepressive effect may be due to the ability of the herb to inhibit re-uptake of serotonin and other neurotransmitters.[84]

St. John's wort interferes with the therapeutic mechanisms of a variety of pharmaceutical drugs including irinotecan (an anti-tumor drug), oral contraceptives, indinavir (a protease inhibitor),[85] and monoamine oxidase inhibitors (MAOI) (anti-hypertensives). These interactions can have serious consequences. For example, the herb can decrease the plasma concentration of cyclosporine levels in organ transplant patients,[86] thus endangering the success of the transplant.[87]

Calcium, an essential mineral, is the major constituent of bones and teeth. It is required for many physiologic activities including muscle contraction, nerve conduction, heartbeat, and blood coagulation. Calcium is generally obtained through the diet. Insufficient calcium intake contributes to reduced bone mass and is a risk factor for osteoporosis.[88]

Though generally considered a beneficial addition to the diet, calcium can interfere with the pharmacokinetics of a number of prescription medications. Orange juice fortified with calcium can decrease the effectiveness of certain antibiotics including ciprofloxacin. The absorption of other quinolone antibiotics, including gatifloxacin and levofloxacin, may also be impacted by excess calcium.[89] Pharmaceutical manufacturers have issued warnings that these medications should not be taken in conjunction with calcium supplements or food products enriched with calcium. For example, the label on the ciprofloxacin bottle states that the drugs should not be taken with milk or calcium-fortified juices.

The interactions caused by concomitant use can often be avoided if patients discuss their supplement use with their conventional medicine practitioners. However, a seminal study estimated that 70 percent of patients do not reveal their herbal remedy use to physicians or pharmacists.[90] Unfortunately, even when they do report their supplement use, some patients cannot accurately describe the ingredients or dosage because products containing the same herb often differ in potency, composition and labeling.[91]

Patients bear only part of the responsibility for discussing dietary supplement use. Despite increased public awareness and government interest, many physicians do not ask their patients about their use of dietary supple-

ments.[92,93] When patients report their dietary supplement use, practitioners should be aware that the supplements "may be bona fide herbal extracts, may be potent pharmaceuticals packaged to resemble herbal extracts, may be herbal extracts adulterated purposely with pharmaceuticals or unintentionally containing heavy metals, or may not be herbal extracts at all."[94]

Many factors hinder effective doctor-patient conversations regarding dietary supplement utilization. As discussed earlier in this chapter, the literature supporting or refuting the safety and efficacy of dietary supplements is evolving. Neither patient nor practitioner may be fully aware of the current state of evidence. Also, because of wide variations in product labeling, neither may be fully aware of what has actually been ingested.[95]

Contraindication

Contraindication refers to any symptom or condition that renders the consumption of a dietary supplement inadvisable for a specific person or group of people. For example, with few exceptions, including folic acid, dietary supplement use is generally not advised during pregnancy because little is known about the placental transmission of most supplements.

A number of dietary supplements are also contraindicated for surgical patients. Morbidity and mortality associated with herbal medications, including heart attack, stroke, and excessive bleeding, may be more likely during the perioperative period[96] because of the potential effects of supplements on the cardiovascular and immune systems, wound healing and drug dosing.[97] Echinacea, ephedra, garlic, ginkgo, ginseng, kava, St. John's wort, and valerian are commonly used herbal supplements that are known to pose a risk during the perioperative period.[98]

Contamination

Contamination can occur at any point in the production cycle of a dietary supplement. Pesticides, herbicides, heavy metals, and bacteria absorbed from groundwater and soil can pollute raw materials. The chemical processes used to extract minerals from rocks and ore can contaminate them,[99] and the processes used to extract and combine active ingredients can contaminate herbs. Heavy metal contaminants including lead, arsenic, and mercury have been found in Ayurvedic herbal medicines[100] and other dietary supplement products.[101] Additionally, the level of manganese in some dietary supplements exceeds the government recommendation for safe consumption of the element.[102]

Dietary supplement products are often compounds of ingredients including herbs, minerals, and animal substances that can augment or attenuate each other's effects. These combinations can lead to adverse health effects. For example, in 1989, a combination sleep aid product containing L-tryptophan was linked to an epidemic of eosinophilia-myalgia syndrome (EMS), a potentially fatal, systemic connective tissue disorder characterized by severe muscle pain, tenosynovitus, edema, skin rash, and neuromuscular disorders. It was the most serious outbreak to date of illness and death caused by a dietary supplement, with 1,500 cases of EMS, including 37 deaths being reported to the Centers for Disease Control and Prevention (CDC).[103] Initial reports suggested that specific L-tryptophan products were contaminated, but additional evidence indicated that it might have been the ingredient L-tryptophan itself that caused or contributed to the development of EMS.[104] As a result, the FDA "[could not] determine that oral dosage forms of [L-tryptophan] and related compounds … can be safely used as dietary supplements."[105]

Adulteration

Adulteration is the intentional addition of undeclared herbs or drugs to dietary supplements. Adulterants are often used to enhance, if not produce, the claimed effect of the product.[106] One of the most egregious cases of adulteration involved two supplements manufactured by BotanicLab of California. BotanicLab marketed the supplements PC-SPES and SPES to treat prostate cancer and bolster the immune system. Approximately 10,000 men with prostate cancer used PC-SPES in 2002.[107]

PC-SPES lots manufactured between 1996 and mid-2001 were adulterated with diethylstilbestrol (DES), a potent synthetic estrogenic drug, and the anti-inflammatory drug indomethacin.[108] DES was once prescribed to prevent miscarriages but in 1971 it was linked to birth defects and the FDA cautioned against its use and added strong warning labels.[109] DES is linked to increased risk of illness in both the mothers who took it and the children they were carrying. Research indicates that mothers have an increased risk of breast cancer, daughters are at increased risk of clear cell adenocarcinoma and infertility, and sons are at increased risk of non-cancerous epididymal cysts.[110]

In February 2002, after conducting an investigation, the Food and Drug Branch of the California Department of Health Services, confirmed that PC-SPES and SPES were adulterated with "undeclared prescription drug ingredients" and warned consumers to stop using the dietary supplements.[111] Lots of PC-SPES contained the anticoagulant warfarin (coumadin) and lots of SPES contained the anxiolytic alprazolam (xanax). BotanicLab voluntarily issued a nationwide recall.[112]

Dosage Inconsistency

Although the therapeutic effect of dietary supplements depends on their potency, there are no federal standards for dosage and purity, and the dose-finding studies that are mandatory for pharmaceuticals are rarely, if ever, performed. For many products, active ingredients have not been identified and the quantity needed to derive an effect has not been determined.[113] Inferior manufacturing practices can lead to inaccuracies in product labeling (products may actually contain greater or lesser amounts of ingredients listed on their label)[114] and the concentrations of active ingredients can vary among and within brands. Consumers may not know how much of any particular ingredient they consume.

Dietary supplement manufacturers are not legally required to use any standardization processes to ensure batch consistency of their products, nor is there any legal or regulatory definition for dietary supplement standardization.[115] Private scientific bodies including the Federation of American Societies for Experimental Biology (FASEB)[116] have attempted to standardize the active ingredient concentration of some dietary supplements. After "an exhaustive study of the available data on amino acids" FASEB found insufficient evidence to establish a safe intake level for amino acids in dietary supplements, and concluded that "their safety should not be assumed."[117] FASEB has also conducted studies on ginkgo biloba extract and chromium picolinate.

Use by Children

Although dietary supplements are not necessary for most healthy children who consume a variety of foods,[118] "many pediatric patients, especially those with chronic or recurrent conditions, use dietary supplements."[119] These supplements are marketed for a host of childhood ailments ranging from ear infections to upper respiratory infections.[120]

With only 45 percent[121] of caregivers discussing their child's use of dietary supplements with their conventional health care provider, pediatricians are often unaware that their patients are taking dietary supplements. This lack of communication puts children at risk because dietary supplement marketing can exacerbate parents' fears regarding pharmaceuticals and lure them away from traditional medical care.

Because it is not legally required, most dietary supplements have not been tested for safety or efficacy in children.[122] There are no dosage guidelines for the administration of dietary supplements to children; therefore, appropriate dosage may be difficult to ascertain. The dosage levels of most dietary supplements are generally set for adult usage, with many children's dosages expressed as fractions of an adult dose. The absorption, distribution, metabolism and excretion of dietary supplements differ in children and adults. In addition, "children may be particularly susceptible to the effects of dosing variations [because] of their smaller size and different capacity for detoxifying chemicals."[123]

Dietary supplement use by children, whether caregiver directed or self-initiated, can be classified in three categories: 1) to derive a health benefit; 2) to enhance physical appearance or athletic performance and; 3) use as alternatives to illegal substances.

Health Benefit

Echinacea and chamomile, both used for respiratory disturbances, were the most frequently used herbs in a 2001 study of patients seen in the pediatric emergency department at the New York Methodist Hospital in Brooklyn.[124] They were also the most commonly used among pediatric surgical patients at Children's Memorial Hospital in Chicago, Illinois.[125] Echinacea, which is "not effective in shortening the duration or decreasing the severity of upper respiratory infections in children,"[126] has been linked to anaphylaxis,[127] rash, and sudden onset of stridor.[128] Chamomile, which may be effective in calming infantile colic,[129] can cause anaphylaxis in children allergic to ragweed.[130,131]

In a study of pediatric cancer patients, dietary supplements, including antioxidant vitamins, were commonly used to prevent and treat non-cancerous conditions such as cold and flu. This adjuvant use could be dangerous because "antioxidants, such as Vitamins C and E, can reduce the effectiveness of chemotherapy [and because] children receiving anti-cancer medications—including cisplatin and anthracyclines—are especially susceptible to cardiac, neurological, and renal impairment. "[132] The concomitant use of dietary supplements can exacerbate these complications.

Enhancing Physical Appearance or Athletic Performance

In one study American adolescents reported a higher prevalence of overweight than any of the European countries or Israel.[133] Consequences of overweight in childhood are often psychosocial.[134,135] "The most immediate consequence of overweight, as perceived by children themselves, is social discrimination."[136] Physical effects include cardiovascular risk factors, such as hypertension, high cholesterol levels, and abnormal glucose tolerance.[137]

It is not clear which weight loss interventions are the most effective for children,[138] but many parents are supplementing or replacing food-portion control and exercise with dietary supplements. Additionally, adolescents with eating disorders frequently use herbal supplements to control their weight.[139]

PediaLoss was a weight loss supplement marketed exclusively for children. Advertisements for PediaLoss claimed that "children can enjoy their favorite foods but with slower absorption of carbohydrates and faster and safer fat burning without using stimulants."[140] In 2004, the Federal Trade Commission (FTC) filed a complaint stating that the manufacturer of PediaLoss "did not possess or rely upon a reasonable basis" when making these claims.[141]

The Skinny Pill for Kids, another weight loss supplement marketed for children ages 6 to 12, contained niacin and a mixture of herb diuretics including uva-ursi, juniper berry, and buchu leaf.[142] When taken as recommended, the Skinny Pill for Kids provided four times the upper limit of niacin recommended for daily ingestion by an eight-year-old.[143] Additionally, the PDR for Herbal Medicine lists uva-ursi as contraindicated for use by children under the age of 12.[144] In January 2004, the FTC filed a complaint in federal district court alleging that "the scientific research to establish that use of the Skinny Pill for Kids causes weight loss in, or is safe for, children 6 to 12 years old is false."[145]

The use of dietary supplements to enhance athletic performance is also common among adolescent[146,147] and college-aged student athletes.[148,149,150] By using supplements, many athletes believe they can gain a competitive advantage without the consequences associated with anabolic steroids or steroid precursors.

Creatine monohydrate (creatine) is one of the most popular dietary supplements used by male and female college athletes.[151,152] In 2004 approximately 28-41 percent of student athletes at National Collegiate Athletic Association (NCAA) institutions used creatine.[153] These athletes use creatine to increase their overall strength and to enhance their ability to complete intense work-out repetitions.[154]

Although most dietary supplements are not illegal, high school and collegiate athletic associations discourage the use of some products and ingredients. The National Federation of State High School Associations warns coaches and school staff not to recommend or distribute any supplements to athletes, and lists creatine as a harmful substance.[155] The supplements bitter orange (citrus aurantium), dehydroepiandrosterone (DHEA), and human growth hormone (HgH) are all included in the 2004-2005 NCAA Banned-Drug Classes list.[156]

Alternatives to Illicit Substances

Some adolescents use dietary supplements as alternatives to illicit substances. Although these alternatives "cannot meet the legal definition of a dietary supplement because they are not intended to supplement the diet, promote health or reduce the risk of disease,"[157] some manufacturers market herbal products as safe sources of a natural high or euphoric feeling. "Adolescents and young adults are particularly easy targets for such promotional tactics."[158] Though not illegal, these substances can impair judgment and increase risk-taking behavior and are therefore considered particularly dangerous for minors.

Legal herbal supplements have been marketed as alternatives for illegal drugs such as gamma-hydroxybutyrate (GHB) and methamphetamine and as alternatives for other intoxicating substances including sedatives and barbiturates. The Partnership for a Drug Free America defines herbal ecstasy as a combination of herbs that are legal, inexpensive, and marketed as a natural high.[159] One "legal high" retailer includes alternatives to speed, mushrooms, and opium among their top ten best sellers.[160]

Unsafe Supplements

The National Toxicology Program (NTP) within the U.S. Department of Health and Human Services[161] selects herbs and active or toxic ingredients found in some herbs for study. These studies focus on characterization of potential adverse health effects, including reproductive toxicity, neurotoxicity, and immunotoxicity, as well as those associated with acute high dose exposure and chronic exposure to lower doses. Studies also look for possible herb/herb and herb/drug interactions and contraindications such as age and pregnancy. Among other supplements, the NTP has studied androstenedione, black cohosh, echinacea purpurea, ginkgo biloba extract, ginseng, and kava extract.

For reasons other than inherent toxicity, the FDA has taken action against a number of supplement products and ingredients that it deemed hazardous to the public's health. For example, the FDA has issued health warnings on liver damage associated with use of the herbal supplements chaparral and germander; kidney failure, seizures and deaths associated with use of yohimbe; and the negative effects of lobelia on the autonomic nervous system.[162] In 2004, Consumers Union[163] listed chaparral, germander, yohimbe, and lobelia on its list of 12 readily available, unsafe supplements that consumers are urged to avoid.[164] The list also included aristolochic acid, kava and comfrey, which have long been under FDA scrutiny.

Aristolochic acid is found in all members of the aristolochia family of botanicals. Aristolochia plants and plant parts are often used as ingredients in traditional Chinese medicines. Often, because the Chinese names for different plants are similar, Aristolochia plants are substituted for other plants including stephania. As indicated below, the substitution can have dangerous consequences.

- More than 100 people who consumed aristolochic acid in a Belgian weight-loss clinic between 1990-1992 experienced nephropathy. At least 70 clients required renal transplant.[165] Later research also confirmed 18 cases of urothelial cancer.[166]

- In the United Kingdom in 1999, two aristolochic acid consumers who were ingesting the supplement to treat eczema experienced "Chinese herb nephropathy" and required renal transplant.[167]

- In 2000, the French Medical Products Safety Agency reported one case of confirmed urothelial cancer, one case of suspected urothelial cancer, and the presence of lymphoma on a graft in consumers of aristolochic acid.[168]

The FDA issued a warning letter to the dietary supplement industry in May 2000 after receiving reports on life-threatening adverse events. Citing carcinogenic and nephrotoxic risks, the FDA advised that products containing aristolochic acid not be allowed to enter the U.S. marketplace.[169] In 2001, the FDA issued another warning regarding the safety of aristolochic acid citing further examples of nephrotoxicity and malignancies.[170] The FDA re-emphasized the need for manufacturers to review their current manufacturing practices and have adequate processes for adverse event collection and reporting.[171] Further, the FDA warned consumers to discontinue use of botanical products that contain aristolochic acid.[172]

FDA has taken no public action on aristolochic acid since 2001; the lack of action apparently is not due to quieted concerns, given that then-Commissioner Mark McClellan announced in January 2004 that the FDA would give more scrutiny to aristolochic acid and two other supplements: bitter orange and usnic acid.[173]

Kava is a revered herb in the South Pacific islands where it is used for traditional ceremonial purposes and as a medicinal relaxant.[174] American consumers use kava preparations for "relaxation (e.g., to relieve stress, anxiety,

and tension)" and to relieve insomnia.[175] From November 2001 through November 2002, kava generated more than $34 million in U.S. sales.[176] However, kava is associated with severe liver-related illness and injury.

Regulatory agencies in countries including Canada, France, Germany, Switzerland, and the United Kingdom have taken actions ranging from advising consumers about the potential risks of kava use to banning the sale of kava-containing products.[177] For example, Health Canada does not believe there is enough evidence to support the use of kava-containing products; kava is considered a drug with no acceptable food uses.[178]

In December 2001, the FDA informed healthcare professionals that products containing kava were implicated in Europe in at least 25 cases of serious liver toxicity including hepatitis, cirrhosis, and liver failure.[179] By March 2002, the FDA had received several reports of liver-related injuries, including a report of a previously healthy woman who required liver transplantation after consuming kava.[180] Based on these reports, the FDA warned that persons who have liver disease or liver problems, or persons who are taking drug products that can affect the liver, should consult a physician before using kava-containing dietary supplements.

Other dietary supplements, including comfrey, can endanger consumers long after they stop using the product. Comfrey is a medicinal plant indigenous to Europe. Teas, tablets, tinctures and lotions made from the root and leaves of the herb have been used for hundreds of years as blood purifiers, antiasthmatic agents, and ulcer remedies. A more common, current use of the herb is as an ingredient in oral anti-inflammatory supplements.

In July 2001, the FDA issued a warning letter noting comfrey as a source of pyrrolizidine alkaloids that present a serious health hazard to humans.[181] The pyrrolizidine alkaloids, in addition to being potent liver toxins, are known carcinogens. Based on evidence of the association between pyrrolizidine alkaloids and serious illness and the lack of valid scientific data to establish a safe level of exposure, the FDA declared that comfrey should not be an ingredient in any oral dietary supplement. In December 2003, Health Canada issued a statement advising consumers not to ingest products made with comfrey because they may contain the liver toxin echimidine.[182]

* * *

In summary, credible scientific knowledge about the efficacy and safety of many readily available dietary supplements is either inadequate or unavailable. While some dietary supplements are proven to have beneficial health effects, others are known to cause serious harm. Consumers often take dietary supplements, or give them to their children, at the risk of delaying conventional care and without knowledge of potential interactions with other medications or of contraindications for the supplement's use. There are no legally enforced quality control standards for dietary supplements, which puts consumers at risk of taking contaminated or adulterated products; dosage can vary from bottle to bottle or from pill to pill. Because of these risks, a number of dietary supplements are and should be considered unsafe.

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4. Federal Regulation of Dietary Supplements

Authority to regulate foods and drugs is shared between the federal and state governments. For the sake of national uniformity and ease of interstate commerce, certain aspects of food and drug manufacture, handling, and marketing are subject only to federal regulations. In those cases, Congress has preempted states from imposing their own regulations that vary from federal standards. Other aspects of food and drug regulation are subject to state-by-state variation. States retain their traditional "police powers," which allow them to protect the health and safety of their citizens. States can exercise these powers (via legislation, regulation, or enforcement activities) in areas where the federal government has not preempted independent state activity.

The Food and Drug Administration (FDA) and the Federal Trade Commission (FTC) regulate dietary supplement labeling, advertising, and marketing. The FDA assumes primary responsibility for food and supplement product labeling, while the FTC regulates food and supplement advertising and marketing. The two agencies maintain a cooperative relationship and frequently coordinate enforcement and education efforts.[1]

A Brief History of Food, Drug, and Dietary Supplement Regulation

Major efforts at food and drug regulation did not occur in the United States until the 20th century and often came in the wake of public tragedies resulting from adulterated or otherwise unsafe substances.[2] Early in the century a wide range of proprietary or "patent" medicines was available to consumers, often marketed under exaggerated testimonials and without disclosure of ingredients, though some contained alcohol or narcotics.[3] Often, foods were likewise mislabeled, misdescribed, or adulterated.[4] Public outcry over stockyard conditions, patent medicines, and food contamination led to the passage of the Pure Food and Drug Act (PFDA) of 1906.[5] The PFDA was the first federal statute to address the adulteration and quality of foods and drugs transported in interstate commerce by allowing offending products to be seized and condemned.[6] Under the statute, drugs had to meet standards of purity and quality set forth by committees of physicians and pharmacists or meet individual standards chosen by their manufacturers and stated on their labels. The law also prohibited the adulteration of food by the removal of valuable constituents, the substitution of ingredients, or the addition of harmful ingredients.[7]

In 1938, the Federal Food, Drug, and Cosmetic Act (FDCA) was passed in reaction to the "elixir of sulfanilamide" tragedy, in which a cherry-flavored tonic that included diethylene glycol caused the deaths of at least 73 children.[8] The FDCA required that drugs be tested for safety,[9] but did not require that drugs be effective.[10] Although the 1906 PFDA authorized the government to challenge blatantly false labeling, drug claims that were merely misleading were not prohibited until the FDCA.[11] The FDCA established a category of foods for "special dietary use" and required that the labels on these products indicate their vitamin, mineral, or other content.[12]

The first requirement for proof of drug efficacy appeared in the Harris-Kefauver Amendments to the FDCA in 1962.[13] In the 1950s and early 1960s, the sedative thalidomide was prescribed to pregnant women who subse-

quently gave birth to children with severe birth defects. This tragedy prompted the Amendments.[14] For the first time, the federal government implemented strict scientific requirements for testing drugs prior to marketing. These included preclinical toxicity studies and evidence of efficacy, and controlled clinical trials by qualified researchers.[15] The Amendments also required that the FDA review the efficacy of all drugs approved for marketing between 1938 and 1962.[16]

The FDA focused on safety and wholesomeness of foods marketed for "special dietary uses" and barred false and misleading labels. The FDA often took enforcement actions against vitamins, minerals, and herbs, because they were touted as treating or preventing disease (claims which can only be made for drugs), or as having some effect on the structure and function of the body (claims which could be made for foods but not botanical products).[17] In the 1960s, the FDA and FTC brought hundreds of court actions against misleading nutrition claims and product advertisements, and "undoubtedly expended more enforcement resources in the area of nutrition than in any other single field."[18]

In 1973, the FDA attempted to implement a new dietary reference standard—the U.S. Recommended Daily Allowance—and to restrict the amounts and combinations of vitamins and minerals that could be marketed as dietary supplements. Products with higher levels or different combinations of nutrients would be subject to review by an advisory committee as part of the FDA over-the-counter drug review.[19] After several lawsuits relating to FDA's implementing procedure,[20] the FDA withdrew the regulations.[21] In addition, Congress responded to pressure from vitamin and mineral manufacturers by passing the "Proxmire Amendments" to the FDCA, which invalidated many of the proposed FDA regulations, in 1976.[22] The Proxmire Amendments revoked the FDA authority to classify a vitamin or mineral as a drug solely on the grounds of exceeding potency, or because vitamins and minerals are marketed in irrational combinations.[23]

Following the Proxmire Amendment and in light of setbacks in the courtroom, the FDA scaled back its efforts to regulate dietary supplements.[24] This regulatory environment encouraged the growth of the dietary supplement industry. The number of dietary supplement products and manufacturers grew significantly through the late 1970s and 1980s, accompanied by a growing number of reports of serious illnesses allegedly attributable to particular supplements.[25] During this time, the FDA took action against dietary supplements only when a product's labeling or advertising made claims that the product performed drug functions such as treating a disease.[26]

Congress passed the Nutrition Labeling and Education Act (NLEA) in 1990. The NLEA allows food products to make disease-related health claims if the FDA certifies that the claim is supported by "significant scientific agreement."[27] The FDA has, for example, certified claims regarding the relationship between dietary fat intake and the risk of certain types of cancer.[28] Subsequent regulations issued by the FDA similarly allowed dietary supplement manufacturers to make disease-related health claims under the significant scientific agreement standard.[29] In practice, some conventional foods, but almost no dietary supplements, were able to meet the significant scientific agreement standard for health claims. In the early 1990s, the FDA rejected all but one dietary supplement health claim application.[30]

At the same time, the FDA began interpreting the federal definition of food additives (substances which become a component of or affect the characteristics of a food) to include single-ingredient dietary supplement capsules. This required manufacturers of these dietary supplements to show a reasonable certainty of safety before the FDA would approve sales or determine that the substance was "generally recognized as safe" (GRAS).[31]

The FDA's broad interpretation was ultimately struck down in federal court, however, and its efforts at regulating dietary supplements as food additives proved unsuccessful.[32]

In 1992, after intense advocacy by the dietary supplement industry, Congress passed a one-year moratorium on the application of the NLEA scientific agreement standard to supplements.[33] In response, the FDA reiterated its position that dietary supplement claims ought to be held to the same standard as food claims, and further asserted that some products were inherently drugs and not dietary supplements, and that many dietary supplements should be considered unapproved food additives.[34] In 1994, the FDA indicated that no supplement currently marketed had the scientific support necessary to make a health claim.[35] This stimulated industry, congressional, and consumer support for new legislation that would enable dietary supplement manufacturers to make health-related claims for their products without prior FDA approval.[36]

Dietary Supplement Health and Education Act (DSHEA) of 1994

For dietary supplements, the most significant amendment to the FDCA is the Dietary Supplement Health and Education Act (DSHEA) of 1994.[37] The provisions of DSHEA define and expand the meaning of dietary supplements and dietary ingredients; establish a new framework for assessing safety; outline guidelines for literature displayed where supplements are sold; provide guidelines for the use of claims and nutritional support statements; require ingredient and nutrition labeling; and grant the FDA the authority to establish good manufacturing practice regulations. DSHEA also requires the formation of an executive level Commission on Dietary Supplement Labels and an Office of Dietary Supplements (ODS) within the National Institutes of Health (NIH).

DSHEA defines dietary supplements as products ("other than tobacco") that are intended to supplement the diet, and contain a "dietary ingredient." The dietary ingredient can be a vitamin, mineral, herb, amino acid, a substance used to increase total dietary intake (e.g., an enzyme), concentrate, metabolite, constituent, or extract. This definition is substantially broader than previous definitions of nutritional supplements and foods, as the category now includes substances that are not consumed as foods and have no nutritional value as defined by nutritionists.[38]

DSHEA regulates dietary supplements as a special category of conventional foods. Therefore, pre-market safety approval is not required and most dietary supplements are subject only to post-market regulation.[39] The only exception to this standard is that manufacturers of "new dietary ingredients" (those not sold in a dietary supplement before October 15, 1994) must notify the FDA at least 75 days before marketing these products and must provide the agency with information substantiating the conclusion that a dietary supplement containing the new dietary ingredient is "reasonably expected to be safe."[40] Additionally, DSHEA applies existing food standards for adulteration to dietary supplements but requires that such a determination be based on conditions of use recommended on the product label or, in the absence of such recommendations, on ordinary conditions of use.

Guidelines for Literature, Claims and Labeling

DSHEA established federal product labeling guidelines for dietary supplements and instructed the FDA to issue regulations specifying detailed requirements. The information that must be disclosed on every dietary supplement label includes: serving size; directions for use; net quantity of contents; dietary ingredients that have a Reference Daily Intake (RDI) or Daily Reference Value (DRV), as well as ingredients for which RDIs and DRVs

have not been established; botanical ingredients; proprietary blends; and nutrients required in the labeling of conventional foods.[41] Labels must include a statement of identity containing the words "dietary supplement," and any ingredients not listed in the "Supplement Facts" panel, as well as the name and place of business of the manufacturer, packer, or distributor.[42] However, the law does not require that information about manufacturers and distributors be included on dietary supplement labels—information on one is sufficient.[43] As the Department of Health and Human Services (DHHS) Office of the Inspector General (OIG) has concluded, this can leave both consumers and the FDA uncertain of the identity and location of the manufacturer of a product.[44]

Generally, DSHEA allows the use of various types of statements on the label of dietary supplements, although claims may not be made about the use of a dietary supplement to "diagnose, prevent, mitigate, treat, or cure" a specific disease. DSHEA allows manufacturers to describe a dietary supplement's effect on the "structure or function" of the body or the "well being" achieved by consuming the dietary ingredient. Under DSHEA, manufacturers can make these structure/function claims without prior FDA approval, as long as the label contains the following disclaimer: *"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."* [45]

Further, a "structure/function" claim is one which:

> claims a benefit related to a classic nutrient deficiency disease and discloses the prevalence of such disease in the United States, [or] describes the role of a nutrient or dietary ingredient intended to affect the structure or function in humans, [or] characterizes the documented mechanism by which a nutrient or dietary ingredient acts to maintain such structure or function, or describes general well-being from consumption of a nutrient or dietary ingredient.[46]

"Calcium builds strong bones" is an example of a structure/function claim that does not require FDA approval. In contrast, a statement that a calcium supplement mitigates the effects of osteoporosis is a claim to "diagnose, prevent, mitigate, treat, or cure" a specific disease and would require FDA approval.[47]

Structure/function claims are exempted from the significant scientific agreement standard that health or drug claims must meet.[48] Under DSHEA, manufacturers are required to have evidence that the structure/function claim is truthful and not misleading, but the quality and quantity of substantiating information is not specified in the law. DSHEA does not grant the FDA authority to inspect food or dietary supplement manufacturers' records to verify the substantiation requirement.[49] Manufacturers do not have to disclose to the FDA or consumers the basis for claims regarding the benefits of their products.[50]

In November 2004, the FDA released a draft Guidance Document noting that it intends to apply a substantiation standard of "competent and reliable scientific evidence" to claims relating to the benefits and safety of dietary supplements.[51] Although the new guidelines put industry on notice of a new recommended benchmark for substantiation, the FDA still lacks the regulatory authority to demand substantiating information from manufacturers.

DSHEA does not regulate promotional materials that are displayed where dietary supplements are sold. Publications, articles, and abstracts are not subject to DSHEA labeling restrictions as long as they are displayed separately, are reprinted in their entirety, are not false or misleading, give a "balanced view" of the available scientific information, and do not promote a particular brand of dietary supplement.[52] Thus, though not on a product's label, health/disease claims may be made in literature displayed in retail establishments without significant scientific agreement or FDA approval.[53] Also, the law does not define what constitutes a "balanced

view" of the available information. Even where the only "available scientific information" is non-clinical trials performed by the manufacturer itself, DSHEA allows such information to be displayed.[54]

Federal activity subsequent to DSHEA has also addressed the claims and labeling allowed for dietary supplement products. In 1997, the Food and Drug Administration Modernization Act (FDAMA) was enacted. FDAMA allows "nutrient content claims" to be made for dietary supplements based upon an "authoritative statement" of a scientific body of the federal government or the National Academy of Sciences. Nutrient content claims describe the amount of a nutrient or dietary substance in a product, often using such terms as "good source," "high," "low," and "free."[55]

In the 1999 case of *Pearson v. Shalala*, the U.S. Court of Appeals for the District of Columbia Circuit ruled that, under certain circumstances, the FDA must allow dietary supplement labels to make "qualified" health claims.[56] These are health claims for which there is emerging evidence, but the evidence is not yet sufficient to meet the rigorous significant scientific agreement standard.[57] If the FDA finds that there is more evidence supporting the claim than against it, the FDA may exercise its discretion and allow a qualified health claim indicating that the supporting evidence is still limited.

Since *Pearson*, the FDA has approved nine qualified health claims for food and dietary supplements. These include claims pertaining to cancer (antioxidants and selenium), cardiovascular disease risk (nuts, walnuts, omega-3 fatty acids, B vitamins, and olive oil), cognitive function (soy phosphatidylserine), and neural tube birth defects (folic acid).[58]

Two examples of FDA-approved qualified health claims are:

> Selenium may reduce the risk of certain cancers. Some scientific evidence suggests that consumption of selenium may reduce the risk of certain forms of cancer. However, FDA has determined that this evidence is limited and not conclusive.

and

> As part of a well-balanced diet that is low in saturated fat and cholesterol, Folic Acid, Vitamin B6 and Vitamin B12 may reduce the risk of vascular disease. FDA evaluated the above claim and found that, while it is known that diets low in saturated fat and cholesterol reduce the risk of heart disease and other vascular diseases, the evidence in support of the above claim is inconclusive.[59]

An example of a health claim the FDA did not approve is: "Consumption of 320 mg daily of saw palmetto extract may improve urine flow, reduce nocturia, and reduce voiding urgency associated with mild benign prostatic hyperplasia." The FDA considered this a health or drug claim to cure, mitigate, or treat an existing disease, and the U.S. Court of Appeals for the District of Columbia Circuit upheld the determination.[60] Moreover, the Court found that First Amendment protection of commercial speech did not bar Congress from determining the nature of drug claims.[61]

In response to the qualified health claim requirements established in the *Pearson* case, in December 2002 the FDA announced the Consumer Health Information for Better Nutrition Initiative, which aims to encourage makers of conventional foods and dietary supplements to make accurate claims about health benefits, and to enhance enforcement against marketers who make false or misleading claims.[62] As part of the initiative, in September 2003 the FDA implemented interim procedures for receiving, prioritizing, and responding to qualified health claim petitions.[63]

Some commentators express concern that the labeling and advertising of dietary supplements can mislead

consumers to believe the products treat or cure disease. At least one survey found that substantial numbers of consumers perceive structure/function statements as claims that a product will prevent or mitigate illness.[64] Other surveys indicate that consumers interpret the mention of the FDA in the disclaimer as a statement that the administration has approved the product.[65]

Other commentators observe that the boundary between structure/function claims and health claims is not entirely clear.[66] There is also speculation that manufacturers and marketers ignore the boundaries set by the FDA and FTC. A 2002 study of 34 commercial dietary supplement websites reported that 92 percent claimed that a supplement could prevent cancer, 89 percent claimed that a supplement could treat cancer, and 58 percent claimed that a supplement could cure cancer. The majority of websites claiming cures for cancer through herb use supplied no evidence to support these claims. Fewer than 40 percent recommended that consumers consult a doctor prior to their use of dietary supplements.[67]

In 2003, the OIG assessed supplement labeling and found many deficiencies in current requirements and practices. Specifically, ingredient information is often difficult to interpret, safety information is often incomplete, statements of intended use often provide limited information, and directions for use are often incomplete.[68] Furthermore, information that is provided is often difficult to understand because labels lack a standardized format, display complex language, small font size, and imbalanced information on benefits and risk.[69] Regarding safety information, OIG found that the majority of labels lacked information about adverse reactions or side effects, interactions, maximum dose, or contraindications, and many lacked information about expiration.[70] Most labels failed to make clear which ingredients were active and which ingredients were absorbed by the body; all privately-held formulations reviewed (proprietary blends) lacked information on the amount of individual ingredients.[71]

The OIG recommended a standard template for dietary supplement labeling, including display of known safety information, adequate directions for use, and the production source and batch or lot number.[72] Safety information would include potential concomitant use problems, contraindications, and possible side effects and adverse reactions, as well as warnings to consumers to cease taking a supplement if they experience adverse reactions.[73] These recommendations have not been implemented.

The OIG research reported supplement users to be particularly interested in safety information.[74] Consumer advocates noted that health professionals may lack training about potential interactions, contraindications, or other adverse effects; consumers were particularly concerned about the lack of warnings for women who are pregnant or nursing, and some believed that supplement labels should automatically bear such warnings unless proven to be safe for pregnant or nursing women.[75]

Good Manufacturing Practices

DSHEA empowered the FDA to issue current good manufacturing practices (GMPs) for the dietary supplement industry.[76] These GMPs are to be modeled on current GMPs for food,[77] not pharmaceuticals.[78] In March 2003, the FDA exercised this authority by issuing proposed current GMPs that would establish industry-wide standards to ensure that supplements are manufactured consistently as to identity, purity, quality, strength, and composition. The proposed current GMPs include minimum standards for design and construction of physical plants, quality-control procedures, testing final products and raw materials, handling consumer complaints, and maintaining records. They would apply to all firms (domestic and foreign) that manufacture, package, or hold

dietary supplements or dietary ingredients distributed in the United States; this includes any firm involved in distributing, testing, quality control, packaging, and/or labeling of dietary supplements or dietary ingredients.[79]

The proposed current GMPs do not address the potential efficacy or toxicity of a product's ingredients. They are aimed at preventing harm from super- or subpotency (too much or too little of listed ingredients), drug contaminants, other contaminants (bacteria, pesticide, lead, etc.), wrong ingredients, improper packaging, and mislabeling.[80] To date the FDA has not issued a final rule.[81]

The Commission on Dietary Supplement Labels

DSHEA created the Commission on Dietary Supplement Labels to consider the appropriate legal standard for health/drug claims.[82] In 1997, the Commission issued a report, in which members expressed concern that some "statements of nutritional support" are in fact more akin to health claims and recommended that both dietary supplements and foods alike continue to be held to the "significant scientific agreement" standard for health claims.[83] Members were divided about the appropriateness of structure and function claims that were associated with significant clinical conditions, such as heart disease. Some members believed such claims were a fundamental flaw of DSHEA, creating a loophole for quasi-drug claims.[84] The Commission urged the FDA to take swift enforcement action against potentially unsafe dietary supplements and to improve postmarket surveillance systems.[85]

The Office of Dietary Supplements at the National Institutes of Health

DSHEA authorized the establishment of the Office of Dietary Supplements (ODS) at NIH. The ODS was created in 1995 within NIH's Office of Disease Prevention. ODS does not have a regulatory role; a central purpose of ODS is to promote scientific research on dietary supplements.[86] DSHEA defines ODS' specific responsibilities as follows:

- To explore more fully the potential role of dietary supplements as a significant part of the efforts of the United States to improve health care
- To promote scientific study of the benefits of dietary supplements in maintaining health and preventing chronic disease and other health-related conditions
- To conduct and coordinate scientific research within NIH relating to dietary supplements
- To collect and compile the results of scientific research relating to dietary supplements, including scientific data from foreign sources
- To serve as the principal advisor to the Secretary and to the Assistant Secretary for Health and provide advice to the Director of NIH, the Director of the Centers for Disease Control and Prevention, and the Commissioner of the Food and Drug Administration on issues relating to dietary supplements.[87]

Other Federal Activity

Within the limited provisions of DSHEA, the federal government has made sporadic administrative and regulatory efforts regarding dietary supplement safety and efficacy.

Adverse Event Reporting

One important difference between regulation of pharmaceuticals and dietary supplements is the requirement for reporting adverse events. Manufacturers of prescription drugs and medical devices are required to report adverse events to the FDA through its MedWatch system.[88] There is no such requirement for dietary supplement manufacturers. Because manufacturers of dietary supplements usually need not provide any evidence of safety before these products are sold to consumers, methods for assessing safety once dietary supplements become publicly available are all the more critical.

The FDA defines an adverse event as an illness or injury that may be associated with a dietary supplement (or a range of other products). The person reporting the adverse event need not be certain of a cause/effect relationship between the adverse event and the use of the product. A "serious" adverse event is one that results in any of the following: death, life-threatening illness, hospitalization, disability, congenital anomaly, or medical intervention necessary to prevent permanent injury or damage.[89]

Adverse event reporting is the FDA's main tool for identifying safety problems. However, the FDA system for tracking dietary supplement adverse events is inadequate; deficiencies have been well documented, most significantly in a critical report from the OIG in 2001.[90] The OIG report *Adverse Event Reporting for Dietary Supplements* documented gaps in four critical phases of the FDA system as of 2001: detecting adverse events, following up and obtaining adequate medical and product information related to the event, assessing information, and pursuing appropriate safety actions.

An FDA-commissioned study estimated that less than one percent of all adverse events associated with dietary supplements were reported to the FDA.[91] A principal reason for this deficiency is that manufacturers are not required to report adverse events to the FDA or to any other party. The OIG reported that the FDA received ten reports of adverse events from supplement manufacturers from 1994 to 1999, although roughly 100 million Americans took supplements during those years.

Since they have not been required to collect adverse event information, in the past some manufacturers have possessed no data on adverse events, while others have had information that was not shared with the FDA. For instance, as discussed in Chapter 1, the Department of Justice began a criminal investigation in August 2002 to determine whether Metabolife International, Inc., manufacturer of the ephedra-based product Metabolife 356, had issued false statements to the FDA concerning the existence of adverse event reports. The FDA had unsuccessfully sought to obtain these reports from Metabolife International, Inc., even through litigation, since 1997.[92]

Manufacturers are not the only potential source of adverse event reports, and not the only source from which reporting could be improved. Poison control centers, a network of sites often based in hospitals and academic medical centers and dispersed throughout the states, received more reports than the FDA during the study period of the OIG report. The OIG recommendations include closer cooperation between poison control centers and the FDA adverse event reporting system.

Another source of adverse event reports is the health care provider. Physicians and other providers forwarded fewer than 20 percent of supplement-related reports to the FDA during the OIG study period. Providers have little information that would help them link specific symptoms to supplements, thus making them unlikely to report. In addition, patients may be far less likely to tell providers about dietary supplement use than about use of prescription drugs,[93] again contributing to the difficulty in establishing causality between supplements

and symptoms. Consumers, too, are far less likely to report adverse events associated with herbal remedies than those linked to over-the-counter treatments. Thus, many adverse reactions to herbal remedies go unmonitored, illustrating the need for greater public awareness that adverse reactions to herbal remedies do exist and should be reported.[94] Both providers and consumers might report more events if significant efforts were made to increase their understanding of the potential risks associated with dietary supplements.

The OIG report relied upon the MedWatch database to document a number of deficiencies in the FDA reporting system. When the FDA receives adverse event reports, the quality of information recorded is often very poor.[95] The FDA had difficulty obtaining adequate medical information about a significant number of events that were reported, and product labels and samples were missing from the majority of reports.[96] The FDA could not determine the manufacturer for roughly one-third of the dietary supplements associated with reports.[97] Because of the difficulties obtaining information, OIG recommended that dietary supplement manufacturers be required to register both themselves and their products with the FDA to help in tracking problems and communicating with the industry.[98]

The FDA is empowered to take appropriate action in response to information it receives through its adverse events reporting system. However, the OIG report points out that the FDA took only 32 such actions against dietary supplements during a six-year period. The number of actions the FDA could responsibly take was limited by the aforementioned system deficits. For instance, the FDA proposed a rule in 1997 to require warning labels and dosage limits on ephedra-based dietary supplements. After industry protests, the Government Accounting Office (GAO) issued a report that was highly critical of the FDA data, citing a lack of information about many specific adverse events and the absence of scientific research to substantiate particular dosage limitations. The FDA withdrew the proposal.

In June 2004, U.S. Senator Richard Durbin, who had previously proposed legislation requiring adverse event reporting for supplements, and DSHEA co-author Senator Orrin Hatch agreed on the floor of the U.S. Senate to work together to craft legislation establishing a mandatory reporting system for serious adverse events related to dietary supplements.[99] The Senators discussed the possibility of attaching such a provision to the Anabolic Steroid Control Act, but that law passed Congress without any dietary supplement adverse event language and was signed by President Bush in October 2004. In comments on the Senate floor before the January 2005 confirmation of Michael Leavitt as DHHS Secretary, Durbin noted that Leavitt has promised to review adverse event legislation.[100]

Center for Food Safety and Applied Nutrition Adverse Events Reporting System

Although no person or entity is legally required to report adverse events associated with dietary supplements, the FDA has attempted to improve its adverse events reporting system.[101] In 2003, the FDA Center for Food Safety and Applied Nutrition (CFSAN)—which regulates foods, dietary supplements, cosmetics, and food and color additives—implemented its Adverse Events Reporting System (CAERS).[102] CAERS is a computerized system that integrates information from individual CFSAN offices, from the FDA MedWatch system, and from events reported directly to its website. Reports are categorized, aggregated, and analyzed by CFSAN medical staff for trends and other indicators that FDA action is needed.[103] CAERS staff attempt to contact the source of an adverse event report, whether a medical facility, poison control center, practitioner, or other source. Staff also attempts to contact the person who suffered the event and seek authorization to view their relevant medical records.

CAERS aims to improve upon previous methods of tracking adverse events by creating a mechanism for follow-up on the reported adverse events that facilitates the assessment and comprehensiveness of the information received.[104] CAERS emphasizes the aggregation of reported adverse events to promote more expedient, appropriate policy decisions.[105] However, as a voluntary system, CAERS is only as useful as the number of reports it receives; at the time of CAERS's implementation, one FDA official estimated that voluntary systems receive reports of only one or two percent of adverse events.[106]

Federal Ephedra Regulation

FDA attempted to ban the sale of dietary supplement products that contain ephedrine alkaloids by regulation in 2004.[107] The FDA rule states that dietary supplements containing ephedrine alkaloids present an unreasonable risk of illness or injury when used according to product label instructions (or under conditions of ordinary use) and are therefore considered "adulterated" under Section 402(f)(1)(A) of the FDCA.[108] The rule applied to all ephedra-containing dietary supplements rather than to individual products or brands. As with other products declared "adulterated," the FDA announced it could enforce the ephedra rule through a variety of actions including seizure of the product, injunction against the manufacturers and distributors of such products, and criminal prosecution of violators.[109]

As discussed in Chapter 1, a U.S. District Court in Utah struck down at least part of the FDA ephedra regulation in April 2005.[110] In *Nutraceutical Corp. v. Crawford*, the court ruled that the FDA had improperly used a risk-benefit analysis in determining that all ephedra supplements posed an "unreasonable risk of illness or injury." At the time this report went to press, it appeared that the FDA ban would remain in force against sales of dietary supplements containing more than 10 milligrams of ephedrine alkaloids per recommended daily dose (the amount contained in the "low-dose" ephedra products sold by the plaintiff in the *Nutraceutical* case).

Androstenedione

The sports "supplement" androstenedione ("andro") was reclassified as a controlled substance by the 2004 Anabolic Steroid Control Act.[111] Prior to passage of that bill, and in response to safety concerns raised by consumers, medical organizations and members of Congress, the FDA targeted 23 companies that manufactured, marketed, and distributed products containing andro with warning letters requesting that they cease distribution of andro-based products or face enforcement actions.[112]

The FDA warning letters described dietary supplements containing andro to be adulterated under the FDCA, albeit on different grounds than those on which ephedrine alkaloid supplements were declared adulterated. The FDA warning letters classified andro supplements as containing "new dietary ingredients." Products containing andro failed to meet the safety requirements for dietary supplements containing new dietary ingredients, and therefore could not be legally marketed.[113]

Enforcement of Labeling, Advertising and Marketing Standards

The FTC enforces federal consumer protection laws, which address fraud, deception, and unfair business practices. When the FTC identifies a violation—e.g., claims for products with unproven benefits, claims to

treat or cure serious diseases, or claims which present significant safety concerns for consumers—it may obtain voluntary compliance by entering into a consent order with the company, pursue an administrative agency action before an administrative law judge, or bring an action in federal court. Depending on the type of action, the FTC may secure a cease and desist order and/or civil penalties.[114]

While the FDA assumes primary responsibility for dietary supplement labeling, the FTC assumes primary responsibility for advertising, including supplement advertising on the Internet.[115] In recent years the two agencies have brought coordinated actions against supplement companies who violate both advertising and labeling guidelines and they chair an interagency health fraud steering committee which includes U.S., Canadian, and Mexican agencies.[116] The FTC and the FDA have also produced various publications to educate consumers on how to spot deceptive advertising and avoid falling prey to unscrupulous marketing of health-care products, including supplements.[117]

Though its enforcement resources are limited, the FDA has taken a number of actions against supplement companies in recent years, in addition to those against ephedra and androstenedione. Typically action was taken against products that contained drug ingredients or were marketed as treating disease, or because potentially unsafe products were imported to the United States. The FDA gives highest priority to products it considers a direct hazard to public health. The FDA initially warns the manufacturer or marketer and works with them to correct the problem voluntarily. If this is ineffective, the FDA may request that the marketer recall the product, or may seek injunction and/or seizure through the court.[118]

In December 2002, as part of the Consumer Health Information for Better Nutrition Initiative, the FDA announced enhanced enforcement efforts against misleading health-related claims. Since that time the FDA has increased its actions in priority areas such as misleading claims to treat life-threatening diseases like cancer, lupus, and Severe Acute Respiratory Syndrome (SARS).[119] As part of that effort, the FDA reports improved cooperation with the FTC in identifying the worst offenders and coordinating enforcement actions. For instance, in June 2003, the two agencies initiated joint actions against two manufacturers of seasilver, a supplement promoted as a safe and effective treatment for 650 serious diseases including AIDS, cancer, and diabetes.[120] In March 2004, both manufacturers agreed to cease manufacture and distribution of the products.[121]

"Operation Cure.All" is an ongoing collaboration between the FDA and the FTC. Through coordination of the activities of the FDA, FTC, Health Canada, and various state Attorneys General, "Operation Cure.All" is a law enforcement and consumer education campaign against the fraudulent marketing of dietary supplements and other health products on the Internet.[122] Since the launch of "Operation Cure.All" in 1999, the FDA efforts have resulted in at least 12 product seizures, 11 product recalls, 43 arrests, and 22 convictions.[123] The FTC has brought 13 law enforcement actions against Internet marketers for unsubstantiated health claims and estimates that more than 100 other websites have taken down their sites or removed their claims after the FTC contacted them.[124]

A list of selected FDA enforcement actions from 1994 to 2004 is included in Appendix B.[125]

* * *

Federal regulation of dietary supplements is far from comprehensive. Though some dietary supplements may be used more like drugs than like foods, they are generally regulated as foods. Given the lack of effective federal oversight of the manufacturing process, supplements are regulated less strictly than conventional foods. Manu-

facturers may make claims that dietary supplements affect or maintain the structure or function of the human body, or provide a benefit related to treatment of a classic nutrient deficiency disease, or promote general well being, without having to provide substantiating information to the FDA.

Though a supplement may interfere with drugs taken concurrently, may be contraindicated for certain medical conditions, or may be inherently harmful, its safety usually does not need to be demonstrated before it is marketed. The burden remains on the FDA and FTC to identify dangerous products or misleading claims after they are on the market.

Though federal lawmakers have periodically proposed changes to DSHEA, necessary legislative action has not been forthcoming. Additionally, some members of Congress have worked with the dietary supplement industry to support restrictions on the regulation of dietary supplements. Therefore state-level efforts must fill the regulatory gaps left by DSHEA. Unfortunately, as described in Chapter 5, current regulation by states is also inadequate.

Notes

1. See, e.g., Statement of John M. Taylor, Associate Commissioner for Regulatory Affairs, Food and Drug Administration, Before the Committee on Commerce, United States Senate, October 28, 2003, website: *http://www.fda.gov/ola/2003/dietarysupplements1028.html*, visited December 6, 2004; Prepared Statement of the Federal Trade Commission Before the Committee on Commerce, Science, and Transportation, United States Senate, "The Commission's Role in Policing Deceptive Marketing of Dietary Supplements," October 28, 2003, website: *http://www.ftc.gov/os/2003/10/dietarysupptest.pdf*, visited December 6, 2004. For a review of other federal agencies that also have some responsibility over aspects of food and supplement safety, see FDA Backgrounder, "Food Safety: A Team Approach," September 24, 1998, website: *http://www.cfsan.fda.gov/~lrd/foodteam.html*, visited December 6, 2004.

2. P. Talalay and P. Talalay, "The Importance of Using Scientific Principles in the Development of Medicinal Agents from Plants," *Academic Medicine* 76(2001):240; see J. K. Braman, "Food for Sport or Faustian Bargain: Regulating Performance Enhancing Dietary Supplements," *Cleveland State Law Review* 47(1999):419.

3. Talalay and Talalay, "Scientific Principles," 240; J. Nickell, "Peddling Snake Oil," website: *http://www.csicop.org/sb/9812/snakeoil.html*, visited December 6, 2004. For a discussion of non-medical use of drugs in American history generally, see C. Whitebread, "The History of the Non-Medical Use of Drugs in the United States," speech at the California Judges Association 1995 Annual Conference, website: *http://nepenthes.lycaeum.org/Ludlow/Texts/history.html*, visited December 6, 2004.

4. Talalay and Talalay, "Scientific Principles," 240.

5. Public Law 59-384 (June 30, 1906), codified at U. S. Code (2002), Title 21, Chapter 1, Federal Food and Drugs Act of 1906, §§ 1-5 (repealed). The original act was repealed by Public Law 75-717 (June 25, 1938), establishing the Federal Food, Drug, and Cosmetic Act. See Talalay and Talalay, "Scientific Principles," 420; K. A. Kaczka, "From Herbal Prozac to Mark McGwire's Tonic: How the Dietary Supplement Health and Education Act Changed the Regulatory Landscape for Health Products," *Journal of Contemporary Health Law and Policy* 16(2000):463, 468.

6. Braman, "Food for Sport," 420; Commission on Dietary Supplement Labels, *Report of the Commission on Dietary Supplement Labels*, November 1997, 11, website: *http://web.health.gov/dietsupp*, visited December 2, 2004.

7. P. Hilts, *Protecting America's Health: The FDA, Business, and One Hundred Years of Regulation* (New York: Alfred A. Knopf, 2002), 54.

8. Braman, "Food for Sport," 419; Kaczka, "Prozac to Tonic," 468; Talalay and Talalay, "Scientific Principles," 240.

9. U. S. Code (2002), Title 21, Chapter 9, §§ 301-397.

10. Talalay and Talalay, "Scientific Principles," 240.

11. U. S. Code, Title 21, § 352; M. Gilhooley, "Herbal Remedies and Dietary Supplements: The Boundaries of Drug Claims and Freedom of Choice," *Florida Law Review* 49(1997):672.

12. Commission on Dietary Supplement Labels, Report, 11; see U. S. Code, Title 21, § 355.

13. Public Law No. 87-781, 87th Congress, 2nd Session (October 10, 1962).

14. Gilhooley, "Herbal Remedies," 672; Kaczka, "Prozac to Tonic," 472-473; Talalay and Talalay, "Scientific Principles," 240.

15. Talalay and Talalay, "Scientific Principles," 240-241.

16. Ibid.

17. L. Khatcheressian, "Regulation of Dietary Supplements: Five Years of DSHEA," *Food and Drug Law Journal* 54(1999):624; Braman, "Food for Sport," 421; Gilhooley, "Herbal Remedies," 672.

18. Gilhooley, "Herbal Remedies," 673.

19. J. Swann, "History of the FDA: Trends in the Last Quarter-Century" in *The Historical Guide to American Government*, ed. G. Kurian (New York: Oxford University Press, 1998), 347.

20. See *National Nutritional Foods Association v. Kennedy*, 572 F. 2d 377 (2d Cir. 1978); *National Nutritional Foods Association v. Weinberger*, 512 F.

2d 688 (2d Cir. 1975); *National Nutritional Foods Association v. FDA*, 504 F. 2d 761 (2d Cir. 1974).

21. Swann, "History of the FDA: Trends in the Last Quarter-Century."

22. Commission on Dietary Supplement Labels, *Report*, 11; Institute of Medicine, *Dietary Supplements: A Framework for Evaluating Safety* (Washington, DC: National Academies Press, 2005), 31; Gilhooley, "Herbal Remedies," 674-675.

23. Institute of Medicine, Dietary Supplements, 31; Gilhooley, "Herbal Remedies," 674-675; Commission on Dietary Supplement Labels, *Report* 12.

24. Khatcheressian, "Regulation of Dietary Supplements," 623-624; Gilhooley, "Herbal Remedies," 676.

25. Institute of Medicine, *Dietary Supplements*, 31-32; Gilhooley, "Herbal Remedies," 676-677.

26. Khatcheressian, "Regulation of Dietary Supplements," 624; Gilhooley, "Herbal Remedies," 676; Commission on Dietary Supplement Labels, *Report* 12.

27. Public Law No. 101-535, 101st Congress, 2nd Session (November 8, 1990), codified at U. S. Code, Title 21, §§ 301, 321, 337, 343, 343-1, 345, 371; Commission on Dietary Supplement Labels, *Report*, 12; U.S. Food and Drug Administration, Center for Food Safety and Applied Nutrition, "Claims That Can Be Made," website: *http://www.cfsan.fda.gov/~dms/hclaims.html*, visited December 6, 2004.

28. Code of Federal Regulations (2002), Title 21, § 101.73(a)(2).

29 Code of Federal Regulations (2002), Title 21, §§ 101.14, 101.70.

30. Khatcheressian, "Regulation of Dietary Supplements," 625; Commission on Dietary Supplement Labels, *Report*, 12.

31. Institute of Medicine, *Dietary Supplements*, 30-31. The FDA based its action on the Food Additives Amendment of 1958, which required premarket approval of an additive unless the FDA had sanctioned its use prior to 1958 or it was considered GRAS. Food additives are defined at U.S. Code (2003), Title 21, § 321(s). See Code of Federal Regulations, Title 21, § 170.3(i).

32. Institute of Medicine, *Dietary Supplements*, 31.

33. Dietary Supplement Act of 1992, Public Law No. 102-571 (1992), codified at U. S. Code, Title 21, § 343; Khatcheressian, "Regulation of Dietary Supplements," 625-626; Commission on Dietary Supplement Labels, *Report*, 12-13.

34. Braman, "Food for Sport," 423; Commission on Dietary Supplement Labels, *Report*, 13.

35. Federal Register, Volume 59, No. 2, 395 (1994).

36. Gilhooley, "Herbal Remedies," 678; Commission on Dietary Supplement Labels, *Report*, 13; Talalay and Talalay, "Scientific Principles," 241. On the ephedra debate in the U. S. Congress, see G. Gugliotta, "Unlikely Allies Aid Industry: Harkin, Hatch Are Supplement Users," *The Washington Post*, December 25, 2000, A04; S. Mencimer, "Scorin' With Orrin: How the gentleman from Utah made it easier for kids to buy steroids, speed, and Spanish fly," *The Washington Monthly* 33 (September 2001): 26; L. Cyphers and M. O'Keefe, "More Storm Clouds over Dietary Supplements," *New York Daily News*, August 19, 2001, Sports; G. Gugliotta, "Dietary Supplement Makers Flex Muscle: $15 Billion Industry Fends off Attempts to Regulate over Health Risks," *The Washington Post*, December 25, 2000, A01. For an extensive newspaper series on ephedra, the supplement industry, and its advocates in Congress, see L. Shrieves in *Orlando Sentinel*, "Bad Medicine: The Free-Wheeling Dietary-Supplement Industry Often Packages Misinformation by the Dose," October 22, 2000, A1; "Ephedra Exposed: The Supplement Used To Help Boost Energy and Lose Weight Is one of the Most Problematic and Puzzling," October 23, 2000, A1; "Dietary Supplements Slip Past Laws: The Industry Is Protected by Friends in Congress and a 1994 Bill, Which Freed It from Most Federal Regulation," October 24, 2000, A1and accompanying stories.

37. Dietary Supplement Health and Education Act of 1994, Public Law No. 103-417 (October 25, 1994), codified throughout U. S. Code (2002), Title 21, § 321 et seq. ("DSHEA"). Note: Specific portions of DSHEA are cited herein by their current location as codified in the U. S. Code, Title 21. To see all provisions of DSHEA assembled in a single location (with corresponding cites to each provision's final location in the U. S. Code), see Public Law No. 103-417, cited above in this note.

38. M. Gilhooley, "Deregulation and the Administrative Role: Looking at Dietary Supplements," *Montana Law Review* 62(2001):85, 96.

39. Statement of Lester M. Crawford, D.V.M., Ph.D., Deputy Commissioner, Food and Drug Administration, before the Subcommittee on Oversight of Government Management, Restructuring, and the District of Columbia, United States Senate, October 8, 2002, website: *http://www.FDA.gov/ola/2002/ephedra1008.html*, visited December 6, 2004; Institute of Medicine, *Dietary Supplements*, 37. As one court has written, "DSHEA does not require dietary supplement manufacturers to comply with the post-market product safety monitoring or reporting requirements that the [federal Food, Drug, and Cosmetic Act] requires for drugs." *Nutraceutical Corp. v. Crawford*, No. 2:04 CV 409 TC, 2005 WL 852157, *1 (D. Utah April 13, 2005).

40. The manufacturer can seek to show that there is a history of use or evidence of safety establishing that the ingredient can reasonably be expected to be safe under recommended conditions of use. See U. S. Code (2003), Title 21, §§ 321(ff), 321(ff)(1), 342(f), 350b, 350b(c); U. S. Food and Drug Administration, *New Dietary Ingredients in Dietary Supplements*, February 2001; Institute of Medicine, *Dietary Supplements*, 37. For a review of the FDA's "weapons" against unsafe products, pre- and post-DSHEA, see Kaczka, "Prozac to Tonic," 479-499.

41. Supplement labeling standards may be found at Code of Federal Regulations, Title 21, Chapter 1, § 101.36 (September 23, 1997). In April 2005, the FDA released a nonbinding guidance document on dietary supplement labeling for industry: "Guidance for Industry: A Dietary Supplement Labeling Guide," website: *http://www.cfsan.fda.gov/~dms/dslg-toc.html*, visited April 15, 2005. The document was prepared by FDA's Office of Nutritional Products, Labeling and Dietary Supplements, a division of CFSAN. For an additional overview, see National Institutes of Health, Office of Dietary Supplements, *Dietary Supplements: Background Information*, website: *http://ods.od.nih.gov/factsheets/generalbackground_pf.html*, visited December 6, 2004.

42. Code of Federal Regulations, Title 21, Chapter 1, §§ 101.5, 101.36. See Food and Drug Administration, *Overview of Dietary Supplements*, website: *http://www.cfsan.fda.gov/~dms/ds-oview.html*, visited December 6, 2004.

43. Code of Federal Regulations, Title 21, Chapter 1, §§ 101.5. The regulation simply requires that the entity included (manufacturer, distributor, etc.) be identified as such, e.g., by the words "Distributed by –."

44. U.S. Department of Health and Human Services, Office of the Inspector General, *Adverse Event Reporting For Dietary Supplements: An Inadequate Safety Valve* OEI-01-00-00180, April 2001, ii-iii.

45. U. S. Code, Title 21, § 343(r), (s); Commission on Dietary Supplement Labels, *Report*, 2-3; U. S. Food and Drug Administration, Center for Food Safety and Nutrition, Dietary Supplement Health and Education Act of 1994, December 1, 1995, website: *http://www.cfsan.FDA.gov/~dms/diet-*

supp.html, visited December 7, 2004.

46. U. S. Code (2002), Title 21, § 343(r); see FDA-CFSAN, "Claims That Can Be Made."

47. For an overview of the different types of claims—health, qualified health, structure/function, and nutrient content—that can potentially be made for foods and dietary supplements, and the requirements for making each type, see FDA-CFSAN, "Claims That Can Be Made"; Code of Federal Regulations (2003), Title 21, Part 101, § 101.96. Note that Federal Trade Commission rules do allow claims to treat or prevent disease in supplement advertising, provided that the manufacturer can substantiate them with "competent and reliable scientific evidence." FTC, Bureau of Consumer Protection, *Dietary Supplements: An Advertising Guide for Industry*, April 2001, 3,9, website: *http://www.ftc.gov/bcp/conline/pubs/buspubs/dietsupp.pdf*, visited December 7, 2004. See D. Grady, "FTC Guidelines Restrict Ad Claims for Supplements," *The New York Times*, November 18, 1998, A26.

48. Gilhooley, 62 *Montana Law Review*, 85.

49. Gilhooley, "Herbal Remedies," 695; FDA-CFSAN, "Claims That Can Be Made."

50. U. S. Food and Drug Administration, *Overview of Dietary Supplements*, January 3, 2001; see also Food and Drug Administration, Office of Food Safety and Applied Nutrition website, "Overview," website: *http://www.cfsan.fda.gov/~dms/supplmnt.html*, visited December 6, 2004.

51. FDA Guidance for Industry, "Substantiation for Dietary Supplement Claims Made Under Section 403(r) (6) of the Federal Food, Drug, and Cosmetic Act," October 2004, website: *http://www.cfsan.fda.gov/~dms/dsclmgui.html*, visited December 6, 2004.

52 U. S. Code (2002), Title 21 § 343-2.

53. Ibid. FDA-CFSAN, *Dietary Supplement Health and Education Act of 1994*; Khatcheressian, "Regulation of Dietary Supplements," 627-628; Gilhooley, "Herbal Remedies," 666-667.

54. Khatcheressian, "Regulation of Dietary Supplements," 627-628.

55. Public Law 105-115, 105th Congress, 1st Session (November 21, 1997), codified at U. S. Code, Title 21, § 301 et seq; FDA-CFSAN, "Claims That Can Be Made."

56. 164 F.3d 650 (D.C. Cir. 1999). The case was brought by a dietary supplement manufacturer. The Court ruled that the First Amendment does not allow the FDA to reject potentially misleading health claims unless the FDA can also show that no disclaimer would eliminate the potential deception.

57. FDA-CFSAN, "Claims That Can Be Made." The court in *Pearson* was skeptical of the FDA's claim that health claims lacking "significant scientific agreement" are inherently misleading and that qualifying disclaimers will not cure this problem. *Pearson*, 164 F.3d at 655.

58. FDA-CFSAN/Office of Nutritional Products, Labeling, and Dietary Supplements, "Summary of Qualified Health Claims Permitted," September 2003, updated March 24, 2004, website: *http://www.cfsan.fda.gov/~dms/qhc-sum.html*, visited December 6, 2004.

59. Ibid.

60. *Whitaker v. Thompson*, 353 F.3d 947 (D.C. Cir. 2004).

61. Ibid. The U.S. Supreme Court has declined to hear the case. 125 S. Ct. 310 (Oct. 12, 2004).

62. U.S. Food and Drug Administration, Center for Food Safety and Applied Nutrition, "Consumer Health Information for Better Nutrition Initiative: Task Force Final Report," July 10, 2003, website: *http://www.cfsan.fda.gov/~dms/nuttftoc.html*, visited December 6, 2004; FDA, Dietary Supplement/Food Labeling Electronic Newsletter, April/May 2003 (#5), website: *http://www.cfsan.fda.gov/~listserv/fda-dsfl.log0305*, visited December 6, 2004.

63. U.S. Food and Drug Administration, "FDA Seeks Comment on Ways to Manage Qualified Health Claims," November 21, 2003, website: *http://www.fda.gov/bbs/topics/ANSWERS/2003/ANS01266.html*, visited December 7, 2004.

64. Khatcheressian, "Regulation of Dietary Supplements," 631, citing National Public Radio/Kaiser Family Foundation/Kennedy School of Government Survey on Americans and Dietary Supplements, February 19-25, 1999, Questions 9-10, website: *http://www.npr.org/programs/specials/survey/front.html*.

65. Talalay and Talalay, "Scientific Principles," 241-242.

66. See, e.g., Gilhooley, "Herbal Remedies," 666, 669; Kaczka, "Prozac to Tonic," 485.

67. R. Bonakdar, "Herbal Cancer Cures on the Web: Noncompliance with the Dietary Supplement Health Education Act," *Family Medicine* 34(2002):522-527; see also F. Charatari, "Websites violate US laws banning treatment claims," *British Medical Journal* 323(2001):827.

68. U.S. Department of Health and Human Services, Office of the Inspector General, *Dietary Supplement Labels: An Assessment*, March 2003 (OEI-01-01-00121), website: *http://oig.hhs.gov/oei/reports/oei-01-01-00121.pdf*, visited December 5, 2004, pp. ii-iv.

69. Ibid., ii-iv.

70. Ibid.

71. Ibid.

72. DHHS, Office of the Inspector General, *Dietary Supplement Labels: Key Elements*, March 2003 (OEI-01-01-00120), website: *http://oig.hhs.gov/oei/reports/oei-01-01-00120.pdf*, visited December 7, 2004, 7-16.

73. Ibid., 10.

74. Ibid.

75. DHHS, OIG, *Supplement Labels: An Assessment*, 12; DHHS, OIG, *Supplement Labels: Key Elements*, 10-11.

76. U. S. Code (2003), Title 21, § 342(g).

77. Ibid.

78. T. Hampton, "More Scrutiny for Dietary Supplements?" *Journal of the American Medical Association* 293(2005):27-28.

79. 68 Federal Register 12157, March 13, 2003, website: *http://www.fda.gov/OHRMS/DOCKETS/98fr/03-5401.html*, visited December 3, 2004.

80. Ibid.; "FDA Proposes Labeling and Manufacturing Standards For All Dietary Supplements," March 7, 2003, website: *http://www.fda.gov/bbs/topics/NEWS/dietarysupp/background.html*, visited December 3, 2004.

81. Finalization of a current GMP rule is listed as a high priority in a December projection by FDA's Center for Food Safety and Applied Nutrition.

CFSAN 2005 Program Priorities, website: *http://www.cfsan.fda.gov/~dms/cfsand04.html*; see also FDA Regulatory Strategy, website: *http://www.cfsan.fda.gov/~dms/ds3strat.html*, both visited December 6, 2004.

82. See Commission on Dietary Supplement Labels, *Report*, v., 5.

83. Ibid., 35, 36.

84. Ibid., 37.

85. Ibid., 25-26. The Commission also highlighted the need for additional resources to assist the FDA and state agencies in accumulating sufficient evidence showing unreasonable risk from certain supplements.

86. National Institutes of Health, Office of Dietary Supplements, "Origin and Mandate," website: *http://dietary-supplements.info.nih.gov/showpage.aspx?pageid=2*, visited December 6, 2004; Commission on Dietary Supplement Labels, *Report*, v.

87. National Institutes of Health, Office of Dietary Supplements, "About the Office of Dietary Supplements," website: *http://dietary-supplements.info.nih.gov/about/about_ods.aspx*, visited December 6, 2004.

88. U.S. Food and Drug Administration, "Reporting Adverse Reactions and Medical Product Problems to the FDA," website: *http://www.fda.gov/medwatch/how.htm*, visited December 6, 2004.

89. U.S. Food and Drug Administration, "Instructions for Completing the MedWatch Form 3500, April 27, 2004, website: *http://www.fda.gov/medwatch/report/consumer/instruct.htm*, visited December 6, 2004. See also DHHS, OIG, *Adverse Event Reporting*.

90. DHHS, OIG, *Adverse Event Reporting*.

91. 69 Federal Register 6817 (Response to Comment 50), Feb. 11, 2004.

92. U. S. Food and Drug Administration, "FDA News: Statement from FDA Deputy Commissioner Crawford regarding Metabolife," August 15, 2002, website: *http://www.fda.gov/bbs/topics/NEWS/2002/NEW00828.html*, visited December 3, 2004. In July 2004, a federal grand jury in California issued an eight-count indictment against Metabolife and its founder. The indictment charged the defendants with six counts of making false, fictitious and fraudulent representations to the FDA and two counts of corruptly endeavoring to influence, obstruct and impede proceedings concerning the regulation of dietary supplements containing ephedra. See Office of the United States Attorney, Southern District of California, News Release, July 22, 2004, website: *http://www.usdoj.gov/usao/cas/pr/cas40722.2.pdf*, visited December 3, 2004.

93. See, e.g., American Cancer Society, "When Planning Surgery, Tell Your Doctor About Herbal Supplements," *http://www.cancer.org/docroot/NWS/content/NWS_3_1x_When_Planning_Surgery_Tell_Your_Doctor_about_Herbal_Supplements.asp*, visited January 11, 2005.

94. J. Barnes et al., "Different standards for reporting ADRs to herbal remedies and conventional OTC medicines: face-to-face interviews with 515 users of herbal remedies," *British Journal of Clinical Pharmacology* 45(1998):496-500.

95. DHHS, OIG, *Adverse Event Reporting*.

96. Ibid.

97. Ibid.

98. Ibid.

99. Congressional Record, June 21, 2004, S7077-7086.

100. Congressional Record, January 26, 2005, S537-538.

101. Statement of Lester M. Crawford, October 8, 2002, website: *http://www.FDA.gov/ola/2002/ephedra1008.html*; U. S. Food and Drug Administration, Center for Food Safety and Applied Nutrition, Office of Scientific Analysis and Support, August 29, 2002, *Letter to Stakeholders: Announcing CAERS – the CFSAN Adverse Event Reporting System*, website: *http://www.cfsan.fda.gov/~dms/caersltr.html*, visited December 17, 2004.

102. CAERS began collecting reports in June 2003. Statement of Robert E. Brackett, Ph.D. Director Center for Food Safety and Applied Nutrition, U.S. Food and Drug Administration Before the Committee on Governmental Affairs Subcommittee on Oversight of Government Management, the Federal Workforce, and the District of Columbia, U.S. Senate, June 8, 2004, website: *http://www.fda.gov/ola/2004/dssa0608.html*; FDA Consumer Magazine, "FDA's Response to Food, Dietary Supplement, and Cosmetic Adverse Events," July-August 2003, website: *http://www.fda.gov/fdac/features/2003/403_food.html*, both sites visited December 6, 2004.

103. FDA, "FDA's Response to Food, Dietary Supplement, and Cosmetic Adverse Events."

104. Ibid.

105. Ibid.; "FDA Creating New System for Adverse Event Reports," August 29, 2002, website: *http://www.vpico.com/articlemanager/printerfriendly.aspx?article=7676*, visited December 20, 2004.

106. "FDA tracks the bad stuff," *Government Computer News*, April 19, 2004, website: *http://www.gcn.com/23_8/news/25613-1.html*, visited December 20, 2004. See also C. Palmer, et al., "Adverse events associated with dietary supplements: an observational study," *Lancet* 361(2003): 101-106.

107. U.S. Food and Drug Administration, *Final Rule Declaring Dietary Supplements Containing Ephedrine Alkaloids Adulterated Because They Present an Unreasonable Risk*, 21 Code of Federal Regulations Part 119 [Docket No. 1995N-0304] RIN 0910-AA59, at 69.

108. U.S. Food and Drug Administration, "Questions and Answers about FDA's Actions on Dietary Supplements Containing Ephedrine Alkaloids," Feb 6, 2004, website: *http://www.fda.gov/oc/initiatives/ephedra/february2004/qa_020604.html*, visited December 3, 2004.

109. Ibid.; see also FDCA § 402(f)(1)(a).

110. *Nutraceutical Corp. v. Crawford*, No. 2:04 CV 409 TC, 2005 WL 852157 (D. Utah April 13, 2005).

111. Anabolic Steroid Control Act of 2004, Public Law No. 108-358, § 2(a)(1)(B) (October 22, 2004).

112. U.S. Department of Health and Human Services, "HHS Launches Crackdown on Products Containing Andro," March 11, 2004, website: http://www.fda.gov/bbs/topics/news/2004/hhs_031104.html, visited December 1, 2004.

113. U.S. Food and Drug Administration, "Crackdown on 'Andro' Products," website: *http://www.fda.gov/fdac/features/2004/304_andro.html*, visited December 1, 2004.

114. Federal Trade Commission, *How the FTC Brings an Action*, website: *http://www.ftc.gov/ftc/action.htm*, visited December 14, 2004. A complete list of dietary supplement-related civil actions filed and consent orders obtained by the FTC from 1984 through July 15, 2003, website *http://www.ftc.gov/bcp/reports/dietadvertisingcases.htm*, visited December 14, 2004.

115. The agencies divide responsibility under a liaison agreement. Working Agreement Between FTC and FDA, 3 Trade Reg. Rep. (CCH) ¶ 9,859.01 (1971). Though the agreement does not refer explicitly to dietary supplements, staff at the FTC's Bureau of Consumer Protection indicates that the agencies follow the same division of roles for supplements as they have done for food products. Comments of the Staff of the Bureau of Consumer Protection, FTC, Before the Department of Health & Human Services, FDA, I*n the Matter of Regulations on Statements Made for Dietary Supplements Concerning the Effect of the Product on the Structure or Function of the Body; Proposed Rule*, Docket No. 98N-0044, August 27, 1998, note 1, website: *http://www.ftc.gov/be/v980023.htm*, visited April 9, 2004. See generally Taylor statement, October 28, 2003; FTC Prepared Statement, October 28, 2003.

116. U.S. Food and Drug Administration, *Dietary Supplement Enforcement Report: July 2003*, July 2003, website: *http://www.fda.gov/oc/whitepapers/chbn_summary.html*. See, e.g., Federal Trade Commission, Operation Cure.All website: *http://www.ftc.gov/bcp/conline/edcams/cureall*; "No Silver Lining for Marketers of Bogus Supplement," June 19, 2003, website: *http://www.ftc.gov/opa/2003/06/seasilver.htm*; "FTC and FDA Take New Actions in Fight Against Deceptive Marketing," June 10, 2003, website: *http://www.ftc.gov/opa/2003/06/trudeau.htm*, all visited December 1, 2004.

117. See, e.g., Federal Trade Commission, "'Miracle' Health Claims: Add a Dose of Skepticism," September 2001, website: *http://www.ftc.gov/bcp/conline/pubs/health/frdheal.htm*, visited December 1, 2004.

118. Crawford statement, October 8, 2002; Brackett statement, June 8, 2004.

119. FDA, *Dietary Supplement Enforcement Report*: July 2003.

120. Ibid.

121. U.S. Food and Drug Administration, "FDA News: Dietary Supplement Firms, Seasilver USA, Inc., and Americaloe, Inc., Sign Consent Decree With FDA To Stop Selling Product Claiming To Cure "Over 650" Diseases," website: *http://www.fda.gov/bbs/topics/news/2004/NEW01037.html*, visited December 1, 2004.

122. U.S. Food and Drug Administration, "Protecting the Public Health: FDA Pursues an Aggressive Enforcement Strategy, June 30, 2003, website: *http://www.fda.gov/oc/whitepapers/enforce.html*, visited December 1, 2004.

123. U.S. Food and Drug Administration, FDA Consumer magazine, September-October 2001, "Agencies Team Up in War Against Internet Health Fraud," September/October 2001, website: *http://www.fda.gov/fdac/features/2001/501_war.html*, visited December 1, 2004.

124. Ibid.

125. FTC cases related to dietary supplements are listed at two websites: *http://www.ftc.gov/bcp/reports/dietadvertisingcases.htm* (listing advertising cases from 1984 through July 15, 2003) and *http://www.ftc.gov/ftc/formal.htm*.

5. State Regulation and Private Sector Initiatives

States have substantial authority to regulate many health and safety matters to their own standards and specifications.[1] However, few states have exercised their traditional health and safety authority to enact restrictions on the manufacture, marketing, and sale of dietary supplements. Many states impose no regulation beyond that required by federal law. Those that have attempted state-level regulation have, for the most part, followed one or both of two tracks: 1) labeling and marketing requirements that supplement federal requirements, and/or 2) restrictions on the distribution and sale of particular dietary supplements. Prior to the 2004 FDA action on ephedra, most state-level regulations had dealt specifically with ephedra-based dietary supplements.

This chapter reviews the scope of state power to regulate dietary supplement manufacture, marketing, and sales, and discusses regulatory actions taken in New York State and initiatives by private entities.

State Regulation

Federal Preemption of State Law

Under the "Supremacy Clause" in Article VI of the U.S. Constitution, federal law is the supreme law of the land. Congress may legislate only in areas in which it is granted power by the Constitution. Once Congress has validly enacted a law pursuant to its designated powers, such as its power to regulate interstate commerce in food or medicinal products, a state law that conflicts with either the letter or policy of the federal law is invalid as a matter of preemption. Sometimes, Congress occupies an entire field or subject area, and then any state regulation in the field may be preempted.[2]

Preemption is always a matter of congressional intention. If Congress wants to exclude state legislation that lies within the federal domain, its intention governs. Sometimes, Congress makes its intent to exclude parallel state legislation explicit, as it did with regard to nutritional labeling pursuant to the Nutrition Labeling and Education Act (NLEA).[3] In the absence of an explicit congressional determination about preemption, Congress' intent must be inferred. With regard to health and safety regulations, Congress often sets a federal minimum intending to leave room for additional state regulation. Sometimes, though, Congress perceives a need for national uniformity and itself balances commercial and safety needs, in order to create an exclusive federal regulatory regime.

State laws may conflict with federal laws in a variety of ways. When there is a clear and direct conflict, state law will be preempted. Conflict may arise when it is impossible for a citizen or legal entity to comply simultaneously with one law without violating the other, or where the laws are otherwise directly contradictory.[4] If a state law penalizes or discourages conduct that federal law specifically seeks to encourage, courts will likely strike down the state law.[5] Likewise, where an individual state action interferes with a federal policy that supports national uniformity, it will likely be struck down.[6]

State laws may also conflict where Congress has "occupied the field" by reserving for itself an entire area of regulation. Where Congress has occupied an entire field, even state regulation that does not conflict in any way with the federal scheme will be invalidated.[7] Federal courts, however, will rule that Congress has occupied a field only where they find clear congressional intent to do so. Such clarity is not often found in federal legislation.[8] In the absence of a clear statement of congressional intent to occupy the field, courts apply various tests to determine whether prior federal action indicates such congressional intent. A broad federal regulatory scheme that incorporates the majority of a subject area can suggest a federal intent to occupy the field. Courts are more wary of finding federal occupation of the field where there is a less comprehensive scheme, since finding federal occupation in such a case may leave parts of the subject area unregulated by any governmental authority.[9] In some cases, however, deregulation may be the federal purpose, and courts will find a "negative occupation" of the field if there is a clear indication that Congress' intent in deregulating was to leave a regulatory "vacuum" in the entire area.[10]

Courts are less likely to find federal occupation of the field where the subject matter is a local concern that has traditionally fallen under state authority. For example, the Supreme Court stated, "regulation of health and safety matters is primarily, and historically, a matter of local concern."[11]

While health and safety regulations have traditionally been considered local matters, regulation of foods, drugs and dietary supplements has been largely a federal issue. Preliminary questions for a state considering dietary supplement regulation are whether federal law preempts that action, if the action conflicts with the objectives of federal law, or if there is federal occupation of the regulatory field.

Several states have passed legislation to regulate various aspects of the dietary supplement industry. This legislation includes labeling and marketing requirements and restrictions on sale and distribution.[12]

The legality of state-specific labeling requirements may be questioned because the NLEA specified a "national uniform nutrition labeling" provision. The provision explicitly preempted states from enacting food nutrition and content labeling requirements (including labeling claims for health benefits) which vary from the federal requirements already in place in the Food, Drug, and Cosmetic Act (FDCA).[13] The Dietary Supplement Health and Education Act (DSHEA) subsequently amended the FDCA to define dietary supplements as "food[s]" for most federal regulatory purposes.[14] Thus, the NLEA's uniformity requirement applies to dietary supplements and states may not vary from federal nutrition/content labeling requirements.

However, NLEA and DSHEA leave states with significant retained authority to regulate supplement labeling and marketing.[15] The NLEA provides an exemption for labeling statements providing warnings concerning the safety of the food (or supplement) or one of its components.[16] Additionally, states retain the ability to challenge false or misleading labeling and advertising (except where the labeling, though deemed deceptive by the state, conforms to federal requirements with preemptive effect).[17] DSHEA indicates that states may not enact their own standards for nutrition or health-related claims in supplement labeling but it does not broaden NLEA's prior preemption of state action.[18]

Some states have also taken action beyond labeling and marketing, including retail restrictions on certain dietary supplement products[19] and, in one case, imposing batch-testing requirements on ephedra-based dietary supplements.[20]

In New York, with few exceptions, consumers can purchase dietary supplements over the Internet, through mail-order catalogs, and in retail establishments including gyms and pharmacies.[21] New York imposes no labeling

requirements beyond those found in DSHEA and NLEA. The state does not monitor the manufacture of dietary supplements, nor is there a centralized registry of dietary supplement manufacturers located in the State.[22]

Distribution of New York State Regulatory Authority

The New York State Department of Health (DOH) is empowered to protect citizens' health and safety by controlling and supervising the abatement of nuisances affecting or likely to affect public health, and by investigating the sources of disease and mortality.[23] The New York State Department of Agriculture & Markets (DAM) is the chief state authority overseeing food manufacture, production, transportation, storage, marketing, labeling, and distribution. DAM licenses food manufacturers and promulgates food-related good manufacturing practices and record-keeping requirements.[24] DOH and DAM share responsibility for food regulation; DAM generally focuses on manufacture and sale of packaged foods (e.g., canned goods sold in retail stores), while DOH focuses on foods prepared and consumed on-site (e.g., in restaurants).

DAM inspects food manufacturing facilities, but not supplement manufacturing facilities. Neither DOH nor DAM conducts regular off-the-shelf testing for adulteration or contamination of dietary supplement products.[25] However, DOH does have the capability to test products for contamination when necessary. In 1994, investigators from DOH's Bureau of Controlled Substances inspected prepackaged herbal medicine products sold in Chinatown, New York City.[26] These products were analyzed for controlled substances and heavy metals at the DOH Wadsworth Center for Laboratories and Research. More than half contained measurable levels of arsenic, chromium, lead, mercury, or selenium.[27]

The State Attorney General has the power, via the State's Consumer Protection Act, to act against fraudulent or deceptive business practices.[28] The Attorney General has pursued enforcement actions against marketers of exorbitantly overpriced dietary supplements and against supplement marketers who do not deliver prepaid orders. The Attorney General's office forwards serious supplement-related complaints to DOH and the FDA.[29]

The New York State Department of State (DOS) maintains records of most business entities, partnerships, and not-for-profit corporations in the State. While most dietary supplement manufacturers located in New York must register with DOS, they are not required to register specifically as dietary supplement manufacturers. Thus the State has no means of identifying all supplement manufacturers located or doing business in New York.[30]

Additionally, the Office of Regulatory Reform (ORR) within the New York State Department of Health was originally created to support Governor Pataki's regulatory reform agenda and facilitate a more efficient and user-friendly rule making process. Since 1999, ORR has been a central resource for research, policy development, and identification of legal and regulatory issues relating to the practice and use of complementary and alternative medicine including dietary supplements.[31]

Retail Restrictions and Product Seizures

Largely as a result of specific illness, injury, or death, access to some unsafe dietary supplement products has been restricted. For example, in 1996 the existing DOH enforcement infrastructure, including its Bureau of Controlled Substances, cooperated with DAM in enforcement efforts against dietary supplements containing ephedrine alkaloids.[32] Acting by order of Governor George E. Pataki, the Commissioner of Health and the

Commissioner of Agriculture & Markets removed from the shelves and banned the sale of 26 specific herbal products containing ephedrine alkaloids that were marketed to minors as legal alternatives to illegal drugs. Companies marketed these products to youth via the Internet, magazine ads, and displays in health food stores, convenience stores, and drug paraphernalia shops. DOH acted against pills and powders, and DAM acted against carbonated stimulant beverages containing ma huang/ephedra.[33]

Prior to the FDA's 2004 ephedra regulation, New York State had enacted a statewide ban on retail sales of ephedra-based products to any consumer in 2003.[34] This followed action by a number of New York counties including Westchester,[35] Rockland, [36] and Suffolk.[37] Illinois enacted a ban in May 2003.[38] California also banned all sales in October 2003, having previously banned sales to minors and imposed warning labels on ephedra supplements in 2002.[39]

The New York law does not pertain to herbal ephedra dispensed by physicians or practitioners of traditional Asian medicine, as long as it was not dispensed as a dietary supplement for weight loss, bodybuilding, or as an "energy food." Physicians and traditional practitioners are required to demonstrate qualification to use ephedra and other herbs "via evidence of an active certification issued to such individual from an entity accredited by the National Commission of Certifying Agencies."[40]

The FDA ephedra regulation—to the extent it survives the April 2005 federal court ruling in *Nutraceutical Corp. v. Crawford* (see Chapters 1 and 4)—pertains only to products legally defined as dietary supplements and does not require persons selling or dispensing ephedra in a non-supplement form to demonstrate any qualifications.[41] This application presumably renders the federal regulation inapplicable to persons dispensing ephedra in non-supplement form (such as in traditional Asian medicine).[42] The FDA regulation includes no language preempting individual states that wish to provide greater protections for their citizens.[43]

New York State Adverse Event Reporting

As discussed in Chapter 4, adverse events associated with dietary supplements typically are not reported, data collection on supplement-related reports is often insufficient, and follow-up or referral to appropriate state or federal agencies rarely occurs. As on the federal level, a lack of consumer awareness, and a lack of education and incentives to report for medical and CAM professionals contribute to under-reporting.

However, there is no clearly designated New York State entity or system to which dietary supplement adverse events would be reported. Adverse events can be reported to the federal system by contacting the FDA's MedWatch service, where the information will be collected and analyzed within the CAERS system.

Those who wish to report a dietary supplement-related adverse event occasionally contact the New York State Poison Control Network (NYSPCN). NYSPCN is comprised of six regional centers, and provides poison emergency assessment and treatment information. NYSPCN staff members also participate in data collection and sharing, and provide public education, including newsletter articles on the dangers associated with herbal products.[44] NYSPCN centers refer reports to appropriate federal agencies including the FDA, the Consumer Products Safety Commission, the Centers for Disease Control and Prevention, and to local and state health officials.

However, the NYSPCN is not designed for tracking supplement-related adverse events. There are no poison control staff assigned to handle dietary supplement-related adverse event reports. Nor is NYSPCN equipped with any specialized data monitoring system that would allow it to track and analyze dietary-supplement related

adverse events; such a system would be extremely costly to develop and might duplicate federal efforts via the CAERS system.

If New York State chooses to encourage more reporting of dietary supplement-related adverse events, it could focus its efforts either on greater use of the federal MedWatch system, or on the poison control network, or both. The most cost-efficient and effective plan is likely to rely heavily on the newly revamped federal system. Specific Task Force recommendations for adverse event reporting are discussed in Chapter 6.

Selected statements on dietary supplements are available at the following websites:

American Academy of Pediatrics
http://www.aap.org/family/SportsShorts_06.pdf

American Cancer Society
http://www.cancer.org/docroot/MBC/content/MBC_6_2X_Herbs_Vitamins_Minerals_Supplements_and_Antioxidants.asp?sitearea=MBC

American College of Obstetricians and Gynecologists
http://www.acog.org/from_home/publications/press_releases/nr05-31-01.cfm

American Heart Association
http://www.americanheart.org/presenter.jhtml?identifier=4522

American Medical Association
http://www.ama-assn.org/ama/pub/category/13945.html

American Society of Anesthesiologists
http://www.asahq.org/patientEducation/herbPatient.pdf

American Society of Health-System Pharmacists
http://www.ashp.org/bestpractices/MedTherapy/Specific_St_DietSuppl.pdf

Arthritis Foundation
http://www.arthritis.org/conditions/tips_supplements.asp

Council for Responsible Nutrition
http://www.crnusa.org/about_gen.html

International Olympic Committee
http://www.olympic.org/uk/news/media_centre/press_release_uk.asp?id=444

National College Athletic Association
http://www1.ncaa.org/membership/ed_outreach/health-safety/drug_testing/banned_drug_classes.pdf

Public Citizen, The Health Research Group
http://www.citizen.org/hrg/drugs/articles.cfm?ID=5195

United States Anti-Doping Agency
http://www.usantidoping.org/files/active/athletes/athlete%20advisory-approved%20or%20verified%20supplements.pdf

All websites were active as of April 12, 2005.

Private Sector Initiatives

There have been limited instances of private-sector policing of dietary supplements—largely by trade associations and private product-testing organizations—beyond the regulatory requirements imposed by federal or state law.[45]

The American Herbal Products Association, a trade association for the herbal supplement industry, develops "Trade Recommendations" (compliance with which is a condition of membership) and "Guidelines" (compliance with which is not a condition of membership) for manufacturers.[46] Its voluntary guidelines recommend labeling St. John's wort products, for example, with a warning against taking them with prescription drugs without first consulting a physician, or with excessive exposure to UV irradiation.[47] Its mandatory Trade Recommendations include the limitation in labels on kava products warning against use by minors, pregnant or nursing women, and those taking prescription drugs; and a recommendation that no herbal dietary supplement contain aristolochic acid.[48]

The United States Pharmacopeia (USP) is a nongovernmental, standards-setting organization that describes its mission as "advanc[ing] public health by ensuring the quality and consistency of medicines, promoting the safe and proper use of medications, and verifying ingredients in dietary supplements."[49] In 2001, the USP began a Dietary Supplement Verification Program (DSVP), through which manufacturers voluntarily submit their products for testing. The USP-DSVP mark on a label indicates that the USP has tested and verified ingredients, product and manufacturing processes.[50] As of October 1, 2004, the USP had verified 730 dietary supplements as of October 1, 2004.[51]

The Good Housekeeping Institute (GH) requires that supplement manufacturers wishing to use the GH seal or to advertise in the Good Housekeeping magazine submit clinical evidence of both safety and efficacy in order to substantiate all explicit or implicit claims. Manufacturers must also submit evidence of batch consistency, and must state in writing that good manufacturing practices are followed in their facilities. GH tests products for consistency between labeling and actual product contents, and verifies that the supplement disintegrates according to USP guidelines. If approved, the manufacturer is usually granted use of the seal for one year.[52]

* * *

Current state and private sector initiatives do not offset inadequate federal level safeguards. Consumers are insufficiently protected against the known and potential harms of some dietary supplements. New York has the legal and practical ability to improve this situation. The following chapter outlines the Task Force's recommendations for developing a systematic approach to dietary supplement monitoring, public and professional education, and, where necessary, regulation of dietary supplement product.

Notes

1. See, e.g., L. H. Tribe, *American Constitutional Law*, 3d ed., Vol. 1 (New York: Foundation Press, 2000), 1208; *Hillsborough County. v. Automated Medical Laboratories*, 471 U.S. 707, 719 (1985) (holding that "the regulation of health and safety matters is primarily and historically a matter of local concern").

2. See, e.g., Tribe, *American Constitutional Law*, 1172-1173; Constitution of the United States, Article VI. The "Commerce Clause" of Article I, Section 8, of the Constitution grants Congress the power to "regulate Commerce . . . among the several states." Because Congress defines the distribution of federal and state regulatory power with regard to interstate commerce, preemption issues frequently arise with respect to federal laws passed pursuant to the Commerce power. Regulations validly promulgated by federal administrative agencies have the force of federal law, and like federal statutes can preempt conflicting state laws. Tribe, *American Constitutional Law*, 1179.

3. See generally, C. Jordan, "Preemption and Uniform Enforcement of Food Marketing Regulations," *Food and Drug Law Journal* (1994): 401-408;

M. M. Bradley, "The States' Role in Regulating Food Labeling and Advertising: The Effect of the Nutrition Labeling and Education Act of 1990," *Food and Drug Law Journal* (1994): 649-674.

4. Congress will sometimes make its own statute inoperative where such conflicts arise. Tribe, *American Constitutional Law*, 1180.

5. Ibid., 1181-1182, 1184. See, e.g., *Jones v. Rath Packing Co.*, 430 U.S. 519 (1977).

6. Tribe, *American Constitutional Law*, 1185. See, e.g., *Ray v. Atlantic Richfield Co.*, 435 U.S. 151 (1978). In this case, the state statute in question allowed either the state or federal standard to be followed, and thus was not struck down.

7. Tribe, *American Constitutional Law*, 1205.

8. Ibid., 1211.

9. Ibid., 1205.

10. A clear indication of Congress's intent to effectively occupy a field with a legal vacuum is required. See, e.g., *Puerto Rico Dept. of Consumer Affairs v. Isla Petroleum Corp.*, 485 U.S. 495, 501 (1988) (to establish preemption in an area of state police power regulation requires an indication in statutory text, not mere signs of intent elsewhere); Tribe, *American Constitutional Law*, 1207.

11. *Hillsborough*, 471 U.S. at 719; see Tribe, *American Constitutional Law*, 1208. See, e.g., *Committee of Dental Amalgam Mfrs. v. Stratton*, 92 F.3d 807 (9th Cir. 1996) (holding that California's Proposition 65 safety warning for carcinogenic products was not preempted by the Medical Device Amendments to the federal Food, Drug, and Cosmetic Act).

12. See generally, C. Jordan, "Preemption and Uniform Enforcement," 401-408; Bradley, "States' Role," 649-74.

13. States could petition the Secretary of Health and Human Services for exceptions under special circumstances, but otherwise must have "identical" food nutrition labeling requirements. Public Law 101-535 (November 8, 1990), codified at U. S. Code, Title 21, § 343-1 (a), (b); Commission on Dietary Supplement Labels, *Report of the Commission on Dietary Supplement Labels*, November 1997, 11, website: *http://web.health.gov/dietsupp*, visited December 2, 2004.

14. U.S. Code (2003), Title 21, § 321 (ff). This section defines supplements and indicates that they "shall be deemed to be a food" within the meaning of the FDCA except for the purposes of determining what is a drug (as opposed to a food or dietary supplement) under federal law. See U.S. Code (2003), title 21, § 321 (g).

15. See Jordan, "Preemption and Uniform Enforcement," 401; Bradley, "States' Role," 659-660, 671.

16. See Jordan, "Preemption and Uniform Enforcement," 401; Bradley, "States' Role," 659-660, 671.

17. NLEA's list of federal misbranding provisions with preemptive effect (at U.S Code (2003), Title 21, § 343-1 (a)) omits existing provisions regarding false and misleading statements in labeling (at U.S. Code (2003), Title 21, § 343 (a)). Also, the NLEA does not impose any limitation on states' power to regulate the claims made in food advertising. See C. Jordan, "Preemption and Uniform Enforcement," 402.

18. DSHEA adds standards for including claims for nutritional benefits (codified at U.S. Code (2003), Title 21, § 343(r)(6)), and NLEA preemption applies to these (see U.S. Code (2003), Title 21, § 343-1(a)(5)). See "State Official Sees Flaws in Dietary Supplement Act," *Food Labeling News* 3 (September 28, 1995).

19. See, e.g., Illinois Compiled Statutes (2003), Chapter 720, Article II, §§ 602/1, 602/5, 602/10, 602/15, 602/20, 602/25, 602/99; California Health and Safety Code (2003), Division 104, Part 5, Chapter 4, Article 4.5, §§ 110423.100, 110423.101.

20. See Texas Administrative Code (2002), Title 25, Part 1, Chapter 229, § 229.461.

21. In 2001, New York enacted a law adding gamma hydroxybutyric acid (GHB) and similar chemicals (including GBL, a precursor that is metabolized into GHB) to Schedule I of the State's Controlled Substances Schedules, making it illegal to possess except for authorized research purposes. This followed Congress's action adding GHB to the federal Schedule of Controlled Substances (Schedule I) in 2000. These laws were enacted partly in response to illegal sales of these chemicals as "supplements." N.Y. Consolidated Laws (2002), Public Health Law, Article 33, § 3306 (e) Schedule I.

22. Consultation with DOS staff, February 18, 2004. See DOS, Division of Corporations, State Records, and Uniform Commercial Code, website: *http://www.dos.state.ny.us/corp/corpwww.html*, visited August 17, 2004. See also, N.Y.S. Department of State, Counsel's Office, Legal Memorandum CO01, "'Doing Business' in New York: An Introduction to Qualification," February 2000, website: *http://www.dos.state.ny.us/cnsl/do_bus.html*, visited August 17, 2004. Pursuant to the Public Health Security and Bioterrorism Preparedness Act of 2002, the FDA implemented a federal registry for domestic and foreign facilities that manufacture, process, pack, or hold food. Dietary supplement and ingredients are included among the food categories captured by the registry. Most facilities are required to disclose the type of their food product; however, facilities manufacturing or otherwise related to "herbals and botanicals" are not required to disclose. See "Food Facility Registration Form," website: *http://vm.cfsan.fda.gov/~furls/frm3537.pdf*, visited January 6, 2005.

23. N.Y. Consolidated Laws (2002), Public Health Law, Article 2, § 201(1)(n), 206(1)(d), Article 13, § 1300

24. N.Y. Consolidated Laws (2002), Agriculture and Markets Law, Article 1, §§ 5, 16, 251-z-1, 251-z-2, 251-z-8, 251-z-9. See N.Y. Codes, Rules, and Regulations (2002), Title 1, Chapter VI, Subchapter F, § 276.1, 276.2.

25. Correspondence with DAM, Office of General Counsel, February 9, 2005, and communication with staff at DOH have been of assistance with regard to current DAM and DOH practice.

26. N.Y. State Department of Health, Bureau of Toxic Substance Assessment, Summary of Findings, July 25, 1996.

27. Ibid.

28. N.Y. Consolidated Laws (2002), General Business Law, Article 22-A, § 349.

29. Staff at the Office of the Attorney General, Bureau of Consumer Frauds and Protection has been of assistance with regard to current enforcement practices of the Office.

30. See DOS, Division of Corporations, State Records, and Uniform Commercial Code, website: *http://www.dos.state.ny.us/corp/corpwww.html*, visited August 17, 2004. For guidance on this question, see DOS legal memorandum, "Doing Business," February 2000.

31. Consultation with Margaret Buhrmaster, New York State Department of Health Office of Regulatory Reform, August 2, 2004.

32. See Press Release, "Governor Protects Consumers from Products Containing Dangerous Herb," May 23, 1996, website: *http://www.state.ny.us/governor/press/may23.html*, visited August 17, 2004.

33. Correspondence with DAM, Office of General Counsel, February 9, 2005 (regarding DAM enforcement). Staff at DOH and the Office of Regulatory Reform have been of assistance with regard to current DOH policy and the 1996 DOH/DAM enforcement action. See also "Governor Protects Consumers," May 23, 1996. Under New York law, it is unlawful to sell "imitation controlled substances." N.Y. State Consolidated Laws (2003), Public Health Law § 3383.

34. N.Y. Consolidated Laws (2003), General Business Law § 391-o. The law prohibited sale or promotional distribution of dietary supplements "containing any quantity of ephedrine alkaloids within New York State." Sellers violating the act (whether persons, partnerships, or corporate entities) are subject to a maximum civil penalty of $500 per violation. Sellers can avoid penalty by demonstrating that they did not have knowledge that the supplement containing ephedrine alkaloids, and that this knowledge was not reasonably available.

35. "Westchester, state lead ephedra ban," *The Journal News*, December 31, 2003, website: *http://www.nyjournalnews.com/newsroom/123103/a0131ephedra.html*, visited December 2, 2004.

36. Local Law No. 8 of 2003, County of Rockland, State of New York, website: *http://www.co.rockland.ny.us/Legislature/Local/law_8_2003.pdf*.

37. Press release, February 11, 2003, website: *http://www.Legislatorcooper.com/pressrelease_153.html*, visited August 17, 2004.

38. Ephedra Prohibition Act, Illinois Compiled Statutes (2003), Chapter 720, Article II, §§ 602/1, 602/5, 602/10, 602/15, 602/20, 602/25, 602/99.

39. California Health and Safety Code (2003), Division 104, Part 5, Chapter 4, Article 4.5, §§ 110423.100, 110423.101.

40. N.Y. Consolidated Laws (2003), General Business Law § 391-o.

41. U.S. Department of Health and Human Services, "Final Rule Declaring Dietary Supplements Containing Ephedrine Alkaloids Adulterated Because They Present an Unreasonable Risk," 69 Federal Register 6788, 6814 (February 11, 2004).

42. Ibid.

43. Ibid.

44. New York State Poison Control Network Annual Report 1999 Data, website: *http://www.health.state.ny.us/nysdoh/poisoncontrol/index.htm*, visited December 2, 2004.

45. For a review of various organizations that have considered the safety and efficacy of dietary supplement ingredients, and an analysis of different approaches to dietary supplement evaluation, see Institute of Medicine, *Dietary Supplements: A Framework for Evaluating Safety*, (Washington, DC, National Academy Press 2005), 66-79.

46. American Herbal Products Association, website: *http://www.ahpa.org/*, visited August 19, 2004. AHPA's Guidelines are posted at *http://www.ahpa.org/guidelines.htm*.

47. Ibid.

48. The Recommendations can be found in the "Code of Ethics" section at the American Herbal Products Association website, *http://www.ahpa.org/policies.htm*, visited February 2005.

49. See United States Pharmacopeia, website: *http://www.usp.org/aboutUSP/uspFactSheet.html*, visited August 24, 2004.

50. Ibid.

51. Dietary Supplement Verification Program, website: *http://www.uspverified.org*, visited March 31, 2005.

52. S. Roan, "Quality Control for Herbs, Vitamins; Consumers: Absent Mandatory Standards for Dietary Supplements, Private Companies are Filling the Void," *Los Angeles Times*, February 7, 2000, S1. Some have expressed concern that such seals and marks may lead consumers to believe, incorrectly, that the supplements have been shown to be both safe and efficacious. A. Peterson, "Finally, Some Help at the Health-Food Store," *The Wall Street Journal*, July 10, 2002, D1. See also Squires, "Making a Claim on Credibility," HE01; Burros, "Eating Well."

6. Recommendations for New York State

I) The New York State Commissioner of Health should create an Expert Committee within the Department of Health to evaluate the safety and efficacy of dietary supplements on an ongoing basis. The Expert Committee will assess available data and make specific recommendations to the Commissioner of Health. The Expert Committee should consider the following policies supported by the Task Force based on current information:

   i) Institute mandatory reporting by dietary supplement manufacturers and distributors of adverse events associated with dietary supplements, with continued support for voluntary reporting by consumers, health care practitioners, and others;

   ii) Create a state-level registry of dietary supplement manufacturers and distributors doing business in New York State, or other equivalent mechanism for 1) assuring compliance with mandatory reporting of adverse events, and 2) facilitating communication with dietary supplement manufacturers and distributors;

   iii) Obtain statutory authorization for the Commissioner of Health to require, by regulation, specific labeling of dietary supplement packaging by manufacturers on such terms as the Commissioner may deem reasonable, and

   iv) Obtain statutory authorization for the Commissioner of Health to ban the sale to minors or to all persons in New York State of specific dietary supplements found by the Commissioner to be unsafe.

II) The Department of Health should undertake a major public health education campaign on dietary supplements, with variations specifically directed to different target groups.

The preceding chapters of this report detail two realities that drive these Task Force recommendations. First, consumers and health care providers have insufficient information about dietary supplements to adequately assess their safety and effectiveness. Second, the Dietary Supplement Health and Education Act of 1994 (DSHEA) curtails the authority of the Food and Drug Administration (FDA) to regulate dietary supplements, and does so to a degree that necessitates state action.

The Task Force recommendations are spurred by concerns similar to those expressed by former FDA Chairman David Kessler in an editorial regarding the agency's inability to respond adequately to dangers posed by supplements containing aristolochic acid:

> [DSHEA] does not require that dietary supplements . . . be shown to be safe or effective before they are marketed. The FDA does not scrutinize a dietary supplement before it enters the marketplace. The agency is permitted to restrict a substance if it poses a "significant and unreasonable" risk under the conditions of use on the label or as commonly consumed.

> The safety standard may sound as if the FDA has all the authority it needs to protect the public. The problem is that the burden of proof lies with the FDA. Even when the agency is able to act, how is it supposed to know which products contain aristolochic acid, and who sells them? What is the agency supposed to tell people who may have consumed these herbs? Congress has put the FDA in the position of being able to act only after the fact and after substantial harm has already occurred.[1]

In the opinion of the Task Force, these concerns apply to the broad range of dietary supplements. Piecemeal federal actions—such as dietary supplement warnings, the pending FDA current Good Manufacturing Practices (GMPs), and the regulation of ephedra-based products—leave consumers unprotected against dietary supplement hazards that may arise in the future. And as demonstrated in the April 2005 federal court ruling in *Nutraceutical Corporation v. Crawford*, DSHEA restrains the FDA even when the agency acts to restrict dietary supplement sales in the interest of public health and in a manner it considers consistent with DSHEA.[2] Additionally, neither federal labeling requirements nor current public education efforts provide consumers with adequate information regarding the risks posed by certain dietary supplement products.

The Task Force is aware that some proponents of federal reform are reluctant to pursue state-by-state regulation. Their concern is that individual state efforts will create a patchwork of regulations that impose undue burdens on industry while leaving consumers at risk. However, in the absence of effective federal regulation, the Task Force supports regulatory intervention by New York State government in order to protect the health and safety of its citizens. New York State has been a leader in this area as demonstrated by the statewide ban on ephedra supplements that preceded federal action.

Because the State needs to strike a balance between protecting the public's health and ensuring consumer freedom, any action taken against unsafe supplements must be supported by reliable evidence. Currently, scientific data to support the safety and efficacy of most dietary supplements is rare and generally of poor quality. Research in the field is ongoing, however, and the status of the evidence is fluid. Therefore, the state approach to dealing with unsafe supplements must be flexible in order to respond to accumulating evidence.

The Task Force acknowledges that not all supplements are unsafe, and many are beneficial. Therefore, strict state restriction should apply only to those supplements that are reasonably demonstrated to pose unwarranted health risks to consumers. A significant degree of consumer freedom is appropriate unless and until reliable evidence suggests otherwise.

The Task Force considers an Expert Committee as the best vehicle for balancing scientific evidence with consumer freedom. The following recommendations offer a vision of this Committee, including policy priorities for consideration. These recommendations will foster systematic evaluation of all available data, therefore allowing New York State to spot trends before they become immediate dangers.

I) The New York State Commissioner of Health should create an Expert Committee within the Department of Health to evaluate the safety and efficacy of dietary supplements on an ongoing basis. The Expert Committee will assess available data and make specific recommendations to the Commissioner of Health.

Data on the safety and efficacy of dietary supplements emerge continually from scientific research, adverse event reports, and other sources. However, information from such varied sources may not come to the attention of regulatory bodies. Therefore, the Task Force recommends that the New York State Commissioner of Health create an Expert Committee to collect and evaluate data on the safety and efficacy of dietary supplements, and to make recommendations to the New York State Department of Health (DOH).

The Expert Committee will serve as an information repository and center of analysis. As data become available, the Committee will evaluate dietary supplements to determine what (if any) danger they present to the public. To review information on the safety and efficacy of dietary supplements appropriately, the Expert Committee will need to utilize a framework for evaluation. The Task Force urges consideration of the "Framework for Evaluating Safety" recently released by the IOM.[3] The Expert Committee could also create its own framework for evaluating dietary supplements.

The Expert Committee's work will result in specific policy or regulatory recommendations to the Commissioner of Health. These recommendations might range from issuing a public advisory, to requiring additional safety warnings on dietary supplement labels, to banning the sale of a particular supplement or supplement ingredient. The recommendations might apply to specific products or to dietary supplements generally; specific options are reviewed in the following sections.

The Expert Committee should consider the following policy supported by the Task Force:

i) Institute mandatory reporting by dietary supplement manufacturers, and distributors of adverse events associated with dietary supplements, with continued support for voluntary reporting by consumers, health care practitioners, and others.

Mandatory reporting of serious adverse events by manufacturers and distributors doing business in New York State will assist the State in promptly identifying and addressing unsafe dietary supplements. Mandatory reporting will enhance the ability of DOH to detect patterns of illness or injury resulting from dietary supplement products.

Both the Institute of Medicine and the White House Commission on Complementary and Alternative Medicine Policy recommended mandatory adverse event reporting at the federal level.[4] As discussed in Chapter 4, these recommendations, now several years old, have yet to be enacted. New York State should require manufacturers and distributors to maintain organized and accessible records of all adverse event reports they receive, with significant sanctions for failure to comply. To verify compliance with mandatory reporting, it is critical to enforcement efforts to be able to access records of reports when investigating a specific supplement-related problem.[5] An adequate federal apparatus for adverse event reporting would likely eliminate the need for a New York requirement; should such federal requirements later emerge, New York manufacturers, and distributors of dietary supplements will already be prepared to comply.

Efficient implementation of mandatory reporting will require the State to clearly articulate its definition of a serious adverse event. The FDA has defined "serious" adverse events associated with medical products as those where use of the product is suspected to have resulted in:

- death;
- substantial risk of death, either at the time of the event or as a suspected result from continued use;
- hospitalization (initial or prolonged);
- disability (significant, persistent, or permanent);
- congenital anomaly following use during pregnancy;
- requiring medical/surgical intervention to prevent permanent impairment or damage.[6]

To define less serious adverse events, the regulations for over-the-counter and prescription drug reporting may offer guidance.[7]

DOH should designate specific staff who will be charged with receiving serious adverse event reports, analyzing data, and forwarding reports to the FDA Center for Food Safety and Applied Nutrition (CFSAN) adverse event reporting system (CAERS) and/or to MedWatch.

In addition to mandatory reporting by manufacturers and distributors doing business in New York, the Commissioner of Health should encourage consumers, health care practitioners, and retailers to report voluntarily all dietary supplement-related adverse events to the FDA MedWatch or CAERS system.[8] Such voluntary reports should include both serious adverse events and less serious events as well. Data on less serious events can be critical in identifying long-term health effects or toxicity from repeated use of supplements that may not cause immediate serious effects. In order to utilize this valuable information, the Expert Committee and designated DOH staff should establish a mechanism for two-way information sharing with FDA MedWatch and/or CAERS staff.

Research suggests that consumers do not report adverse events associated with supplements as frequently as with drugs. A 1998 study found that 26 percent of respondents would consult their doctor for a serious adverse reaction to an over-the-counter medicine, but not to an herbal remedy.[9] To encourage effective voluntary adverse event reporting, DOH must provide education to consumers and health care providers in identifying and addressing supplement-related events, including direct effects of supplements as well as supplement-drug interactions. Both professional and consumer education about adverse event reporting were recommended at the federal level by the Institute of Medicine in its 2005 report.

The Expert Committee should consider the following policy supported by the Task Force:

ii) Create a state-level registry of dietary supplement manufacturers and distributors doing business in New York State, or other equivalent mechanism for 1) assuring compliance with mandatory reporting of adverse events, and 2) facilitating communication with dietary supplement manufacturers and distributors.

One of the largest regulatory gaps left by DSHEA is the FDA's lack of authority to gather adverse event reports from supplement manufacturers and distributors. However, mandatory reporting cannot effectively be accomplished unless the State can identify those entities from which reporting is required.[10] The same information will also be needed to monitor current GMPs when these come into effect. In conducting its own study on GMPs in the supplement industry in 1999, the FDA was not able to confirm that it had identified all supplement manufacturers in New York State, and in fact believed that it had missed a number of smaller manufacturers.[11] Given that a subsequent survey found that small manufacturers were least likely to follow a GMP model,[12] this basic lack of information highlights an additional regulatory gap that New York State must close.

The Expert Committee should consider the potential role of the New York State Department of State (DOS) in assisting with the reporting requirement. DOS maintains records of most business entities, partnerships, and not-for-profit corporations in the State.[13] It also registers, licenses, and regulates various businesses and practices to protect the health, safety, and welfare of consumers.[14] However, the files do not identify which businesses manufacture and/or distribute dietary supplements.[15] Mandating registration with DOS will allow New York State to identify and communicate with all dietary supplement manufacturers doing business in the State. It will enable the State to alert manufacturers to policy changes related to manufacturing and marketing practices and will facilitate enforcement of mandatory adverse event reporting.

Dietary supplement manufacturers doing business in New York could be required to pay a fee in addition to general business registration fees. The DOS could collect this extra fee during the registration process and forward it to DOH to fund dietary supplement related activities (e.g. public education). The fees will help cover

administrative and enforcement costs. The Task Force recognizes the regulatory burdens already imposed on businesses in New York State. However, the state requires a means to monitor compliance with adverse event reporting, as well as with proposed federal manufacturing standards.

The Expert Committee should consider the following policy supported by the Task Force:

iii) Obtain statutory authorization for the Commissioner of Health to require, by regulation, specific labeling of dietary supplement packaging by manufacturers on such terms as the Commissioner may deem reasonable.

Current federal dietary supplement labeling regulations fail to ensure that sufficient information is provided to facilitate consumer understanding.[16] Mandatory state-level labeling can address this problem by (1) alerting consumers that particular products have not been determined to be safe and/or effective, or (2) informing consumers of risks that are reasonably suspected, either because of clinical data or because of associated adverse events.

The power to require dietary supplement labeling should be explicitly assigned by the Legislature to the Commissioner of Health. Vesting supplement labeling authority with the Commissioner of Health will likely require liaison with the State Department of Agriculture & Markets (DAM). Currently, warning labels can be mandated by regulation from the Commissioner of Agriculture & Markets. DAM is empowered to promulgate food labeling regulations (which must comply with federal regulations), and DAM has already adopted federal food labeling regulations that include dietary supplement labeling requirements.[17]

Labeling requirements can be mandated for specific products. For example, the State could require products containing St. John's wort to bear information regarding the serious risks of concomitant use. Other labeling requirements could apply to any dietary supplement sold in the State of New York. For example, the Task Force rejects the blanket assumption of dietary supplement safety during pregnancy and lactation, although the demonstrated safety of some, such as folic acid, is recognized. Therefore, the Expert Committee should recommend that the Commissioner of Health mandate that products that have not been proven safe during pregnancy and lactation carry an appropriate warning label. Also, the Expert Committee should recommend that the Commissioner mandate that the labels of all dietary supplement products sold in New York State bear the FDA MedWatch (adverse event reporting) toll free telephone number.[18] The Expert Committee should assess how New York can access information sent directly to federal authorities, and analyze this data in conjunction with data collected within New York.

The Expert Committee should consider the following policy supported by the Task Force:

iv) Obtain statutory authorization for the Commissioner of Health to ban the sale to minors or to all persons in New York State of specific dietary supplements found by the Commissioner to be unsafe.

The Commissioner of Health has broad power to protect the citizens of New York against public health hazards and some of the proposed actions require no new grant of authority.[19] Within current authority the Commissioner can undertake other regulatory actions at least on a temporary basis in urgent situations.[20] For instance, the Commissioner may currently order people or entities to cease dangerous activities, such as the sale of a hazardous product. However, this authority requires written notice to each entity that is engaging in the dangerous activity; these entities are then permitted a hearing in not more than 15 days.[21] This authority is unwieldy as a means of banning sales of an entire class of products, as opposed to a single brand manufactured by one company.

New York State should authorize the Commissioner of Health to ban sales by means of a general order or emergency declaration, without the requirement to identify and serve each entity with an order. This order could be followed by a period of public comment, during which business entities will have the opportunity to be heard. At the close of the comment period, the Commissioner may choose to maintain, revise, or rescind the emergency order. Such a ban might apply to minors only, or to all consumers in New York State. The Commissioner might exercise this new authority upon evaluation of valid evidence indicating unwarranted health risks posed by particular dietary supplements or supplement ingredients.

Banning the sale of specific unsafe dietary supplements to minors.

The ability of adults to make informed choices is generally presumed. Where minors are concerned, however, the assumption is different. Under the doctrine of *parens patriae*, the state accepts an obligation to protect children, in part by restricting minors' access to various products and services. The state might premise a restriction on the greater danger of physical harm to children's developing bodies, or on the presumption that minors may lack the experience and judgment to use a product responsibly.

Prior to the federal ephedra ban, a few states prohibited the sale or furnishing of foods or supplements containing ephedrine alkaloids to minors.[22] At least one state prohibits public school employees from selling or distributing to students any dietary supplement containing a "performance-enhancing compound," or from endorsing or suggesting the ingestion thereof.[23] New York's 1996 action against certain ephedra products, discussed in Chapter 5, was the result of the products being marketed to youth as alternatives to illegal drugs.[24]

The Legislature should empower the Commissioner of Health to impose retail restrictions on minors' ability to purchase dietary supplement products reasonably believed to present significant dangers to their health. The Expert Committee should review promptly the evidence for banning the sale to minors of dietary supplements that are marketed as legal alternatives to illegal drugs. Such products can contain combinations of a wide variety of ingredients whose safety in combination is unverified; one FDA safety warning concerned a product marketed as a dietary supplement producing a "legal high," but containing the controlled substances GBL and GHB, as well as sedatives and ephedrine.[25]

Effective regulation of dietary supplements marketed to, or particularly attractive to, minors will require liaison between DOH and other relevant state agencies, particularly the New York State Education Department (NYSED). Prohibition of the sale of certain dietary supplements to minors, would, for instance, ideally be accompanied by equivalent regulation by the NYSED prohibiting school employees from distributing such supplements to elementary or secondary students.

Banning the sale of unsafe dietary supplements to all consumers in New York State.

There is no general guideline for determining when a dietary supplement warrants a retail ban.[26] Some factors to be considered are patterns of use or misuse among both minor and adult consumers, overall sales (taken as evidence of the number of affected consumers), and the quality of clinical and/or adverse event report evidence suggesting danger. If a supplement were found to present such a risk of harm that removal from shelves were warranted, the State could act to protect the public from imminent health hazards.

Few dietary supplements are expected to present a degree of danger warranting a retail ban. However, the Expert Committee should urgently review available data and consider actions regarding the sale and/or labeling of kava, aristolochic acid, and comfrey in New York State.

II. The Department of Health should undertake a major public health education campaign on dietary supplements, with variations specifically directed to different target groups.

The Commissioner of Health should publicly disseminate information regarding the safety and efficacy of dietary supplements. DOH currently devotes considerable effort to communicating beneficial health-related information to the public, but it has very rarely communicated dietary supplement-related information.[27] Public advisories may be most appropriate concerning individual products or classes of products, or to create a rapid public alert to an emerging problem.

DOH should undertake a broad public education campaign. The public education campaign should focus on providing general information about supplement risks and benefits, as well as guidance for consumers in deciding whether to purchase supplements and how to respond to adverse health effects arising from supplement use.

DOH could collaborate with appropriate professional bodies and educational institutions to undertake a dietary supplement education program. Such a campaign might include advisories about specific supplement products, or general information aimed at helping consumers make informed choices about using supplements for themselves or their children. Variations in the curriculum should be specifically directed to different target groups, including physicians and other healthcare professionals, traditional and complementary and alternative medicine practitioners; coaches and educators; parents; and adolescents. The educational campaign will include information on:

- the benefits and risks of dietary supplements;
- the contraindications for dietary supplement use;
- the dangers of concomitant use ;
- the side effects of dietary supplements;
- how to identify and report supplement-related adverse events, including immediate and long-term health effects.

The limits DSHEA places on the federal government's ability to adequately regulate dietary supplements make consumer and professional education critical. Both professionals and consumers lack reliable information about the benefits and risks of dietary supplements. New York State can protect the public health by educating citizens to make safe and informed choices about the health products they purchase.

* * *

These recommendations strike an appropriate balance between two legitimate state purposes: respecting consumer freedom to purchase potentially beneficial products, and protecting the health and safety of those consumers. The proposed Expert Committee on dietary supplements would develop state-level measures for tracking serious adverse events associated with dietary supplements, increasing supplement-related information available to consumers, and reacting to developing scientific literature on dietary supplements. An accompanying DOH education campaign would give consumers and health care providers a broader understanding of the potential risks and benefits associated with dietary supplements, thus allowing New Yorkers to make well-informed choices about dietary supplements.

Notes

1. D. Kessler, "Cancer and Herbs," *New England Journal of Medicine* 342(2000):1742-1743.

2. *Nutraceutical Corp. v. Crawford*, No. 2:04 CV 409 TC, 2005 WL 852157 (D. Utah April 13, 2005).

3. Institute of Medicine, *Dietary Supplements: A Framework for Evaluating Safety*, (Washington, DC: National Academies Press 2005).

4. Institute of Medicine, *Dietary Supplements*, 16. See also White House Commission on Complementary and Alternative Medicine Policy, Final Report, March 2002, website: *http://www.whccamp.hhs.gov/fr10.html*; visited December 7, 2004.

5. Consultation with staff at FDA, Center for Food Safety and Applied Nutrition, February 27, 2004.

6. See "What Is A Serious Adverse Event?" website: *http://www.fda.gov/medwatch/report/DESK/advevnt.htm*, visited February 26, 2004.

7. Code of Federal Regulations, Title 21, § 314.80.

8. As discussed in Chapter 4, supplement-related reports received by MedWatch are forwarded to the FDA's CAERS for analysis and follow-up.

9. J. Barnes, et al., "Different Standards for reporting ADRs to herbal remedies and conventional OTC medicines: face-to-face interviews with 515 users of herbal remedies," *British Journal of Clinical Pharmacology* 45(1998):496-500.

10. Nebraska required manufacturers and distributors of ephedrine-containing supplements to register with the state and pay a registration fee; this law was intended to expire when FDA implements current GMPs. Revised Statutes of Nebraska (2002), Chapter 28, Article 4, § 28-454.

11. Communication with staff at FDA, Center for Food Safety and Applied Nutrition, February 24, 2004. See S. A. Cates et al., "Survey of Manufacturing Practices in the Dietary Supplement Industry: Final Report," Research Triangle Institute (Research Triangle Park: May 17, 2000), RTI Project Number 6673-6, website: *http://www.foodriskclearinghouse.umd.edu//Doc/Dietary_Supplement_Survey.pdf*, visited February 25, 2004.

12. Cates et al., "Survey of Manufacturing Practices," D-6.

13. See Department of State, Division of Corporations, State Records, and Uniform Commercial Code, website: *http://www.dos.state.ny.us/corp/corpwww.html*, visited January 12, 2004.

14. See Department of State, Office of Business and Licensing Services, Mission, website: *http://www.dos.state.ny.us/lcns/licensing.html*, visited January 15, 2004.

15. Consultation with staff at Department of State, Counsel's Office, February 18, 2004.

16. U.S. Department of Health and Human Services, Office of Inspector General, *Dietary Supplement Labels: An Assessment*, March, 2003, 12-14; see DHHS, OIG, *Supplement Labels: Key Elements*, March, 2003, 10-11.

17. New York Codes, Rules and Regulations (2002), Title 1, Chapter VI, Subchapter C, § 259.1. See, e.g., Code of Federal Regulations (2002), Title 21, Chapter I, Subchapter B, Part 101, §§ 101.70 et seq. See also U.S. Code (2003), Title 21, §§ 321 (g), (ff), indicating generally that dietary supplements "shall be deemed to be a food" within the meaning of the Food, Drug, and Cosmetic Act except for the purposes of determining what is a drug (as opposed to a conventional food or dietary supplement) under federal law.

18. See Institute of Medicine, *Dietary Supplements*.

19. The general powers and duties of the Commissioner of Health are found at New York Consolidated Laws (2003), Public Health Law, § 206. See generally, L. O. Gostin, Public Health Law: Power, Duty, Restraint, (Berkeley: University of California Press, 2000).

20. See New York Consolidated Laws (2003), Public Health Law § 16. Cf. Public Health Law § 12-a, outlining the non-emergency process for investigating potential public health hazards.

21. New York Consolidated Laws (2003), Public Health Law § 16.

22. E.g., California Health and Safety Code (2002), § 110423; Michigan Complied Laws (2002), Chapter 333, Public Health Code, Article 7, Part 73, § 333.7339; Revised Statutes of Nebraska (2002), Chapter 28, Article 4, § 28-448; Texas Administrative Code (2002), Title 25, Part 1, Chapter 229, § 229.463; Florida Compiled Statutes, Title XXXII, Chapter 501, § 501.0583; New Jersey Statutes § 24:6H-1.

23. Michigan Compiled Laws, § 380.1317 (1)(a), (1)(b). Exceptions are provided for employees providing otherwise legal supplements to their own children, or providing supplements to students in activities entirely unrelated to school (and with whom the employee has no in-school contacts). Michigan Compiled Laws, § 380.1317 (2)(a), (2)(b). On March 29, 2005, the Oregon Senate passed a similar bill, which was referred to the state House of Representatives. Associated Press, "Senate acts to reduce supplement use by teens," website: *http://159.54.226.83/apps/pbcs.dll/article?AID=/20050330/STATE/503300305/1042*, visited April 6, 2005.

24. See Press Release, Governor Protects Consumers from Products Containing Dangerous Herb, Thursday, May 23, 1996, website: *http://www.state.ny.us/governor/press/may23.html*, visited December 7, 2004.

25. FDA, MedWatch Safety Alert, "Cytotec Solutions, Inc. Products," April 4, 2004, website: *http://www.fda.gov/medwatch/safety/2004/safety04.htm#cytotec*, visited December 7, 2004.

26. Ohio grants the Director of Agriculture the discretion to remove a dietary supplement from the shelves if the product is believed to be adulterated. Ohio Revised Code (2001), Title XXXVII, Chapter 3715.

27. See, e.g., Center for Consumer Healthcare Education, "20 Tips To Help Prevent Medical Errors," website: *http://www.health.state.ny.us/nysdoh/healthinfo/20tips.htm*, visited March 30, 2004; New York State Department of Health, News Release, "Statement from New York State Commissioner of Health Dr. Antonia C. Novello on National Ephedra Ban," December 30, 2003, website: *http://www.health.state.ny.us/nysdoh/commish/2003/ephedra_release_12-30-2003.htm*, visited March 30, 2004. The general functions, powers and duties of the Department of Health, including the duty to promote education in the prevention and control of disease, are found at New York Consolidated Laws (2003), Public Health Law § 201.

Appendix A: Commonly Used Dietary Supplements

Unless otherwise cited, all information is from S.E. Hendler et al., *PDR for Nutritional Supplements*; Second Edition (Montvale, NJ: Medical Economics Company Inc., 2001) and J. Gruenwald, *PDR for Herbal Medicines* (Montvale, NJ: Medical Economics Company, Inc., 2000).

Supplement	Indications	Efficacy	Side Effects	Contraindications	Contamination	Dosage & Purity	Concomitant
Antioxidants Vitamin A (beta carotene), Vitamin C (ascorbic acid), Vitamin E, selenium, carotenoids	General Health	Supplementation with vitamin E, C or multivitamins is not associated with a significant decrease in total cardiovascular disease or coronary heart disease.[1,2,3,4,5,6] May be beneficial for patients with age-related macular degeneration[7,8] but not for the prevention or treatment of cataracts.[9] Studies regarding efficacy in delaying or preventing cognitive impairment,[10] Alzheimer's disease,[11,12] and other neurological diseases[13] are inconsistent.	All antioxidants: yellowing of the skin.[14] Vitamin A: increased risk of osteoporosis,[15] liver damage, elevated intracranial pressure,[16] and birth defects.[17,18] Vitamin C: may cause kidney stones. Vitamin E: associated with increased risk of heart failure;[19] may exacerbate upper respiratory infections,[20] cause bleeding, nausea, and diarrhea.[21] Selenium: selenosis, intestinal discomfort, nerve damage, hair loss, and nail damage.[22]	Vitamin A: Pregnancy and liver disease. Should not be used by children.[23]	No reliable evidence.	For adults, the upper level for daily consumption of vitamin C is 2,000mg, of vitamin E is 1,000mg, and of selenium is 400mg. Most North Americans consume the recommended daily allowance through diet and do not need supplements.[24,25]	Mega-doses of vitamins A and E are the most likely to interact with other medications.[26] Antioxidants are known to interfere with simvastatin and niacin.[27] May reduce the effectiveness of chemotherapy.
Aristolochia	Anticonvulsant	Insufficient reliable information regarding efficacy.[28]	Vomiting, spasms, gastroenteritis, severe kidney damage, nephropathy.[29]	Pregnancy and nursing.[30]	No reliable evidence.	No reliable evidence.	May decrease effectiveness of antacids, H2-blockers, and proton pump inhibitors.
Bitter Orange (orange, neroli, bigarade orange, citrus aurantium)	Weight Loss	Approved in Germany for loss of appetite and dyspeptic complaints.	Increased UV sensitivity.[31]	Pregnancy and nursing. Should not be used by children.[32]	No reliable evidence.	No reliable evidence.	Can prevent specialized enzymes from metabolizing certain medications, increasing the blood levels of many drugs.[33]
Black Cohosh (Cimicifuga racemosa, actaea racemosa, black snakeroot, bugbane, bugwort, rattle snakeroot, macrotys rattleroot, rattletop, rattleweed, Traubensiberkerze, Wanzenkraut)	Menopause	Studies regarding estrogen-like action, such as the alleviation of menopausal symptoms and improvement in premenstrual syndrome are conflicting.[34]	Frontal headaches,[35] minor stomach upset.[36,37]	Pregnancy and nursing, estrogen dependent tumors,[38] and history of breast cancer.[39]	No reliable evidence.	The average recommended dose is 40-80mg per day, with a maximum duration of six months.[40]	Can potentiate effects of antihypertensive medications resulting in hypotension, and can have a synergistic effective with tamoxifen. Concurrent use w/HRT not recommended.[41]
Calcium	Osteoporosis	In a review of 52 trials all but two showed beneficial effects, including better bone balance, greater bone gain during growth, reduced bone loss in the elderly, and reduced risk of fracture.	Gastrointenstinal hemorrhage[42] and irritation, belching, flatulence;[43] increases risk of kidney stones.[44]	Hypercalcemia,[45] sarcoidosis, renal insufficiency, hyperpara-thyroidism,[46] hypothyroidism,[47] hypervitaminosis D.	In one report, eight of the 23 nationally available calcium carbonate products contained small amounts of lead.[48]	Thirty-one of 35 products tested met standards for dosage and purity. The four that failed contained less then the claimed amount of calcium.[49]	May reduce the absorption of biphosphonates,[50] quinolones[51] and tetracyclines.[52] Absorption of calcium may decrease if taken with H2 blockers or proton pump inhibitors[53] and may increase if taken with vitamin D analogues.[54]

Supplement	Indications	Efficacy	Side Effects	Contraindications	Contamination	Dosage & Purity	Concomitant
Chitin (Chitosan)	Weight Loss	Claims that it can reduce weight[55] or affect fat absorption are unsubstantiated.[56,57]	No reliable evidence.	Pregnancy and nursing. Should not be used by children.[58]	No reliable evidence.	There is no pure form; it is always combined with a number of substances.[59]	May slow the absorption of oral contraceptives.[60]
Chondroitin (Chondroitin sulfate, Arth X™ Plus™)	Osteoarthritis	May be useful in the treatment of osteoarthritis.[61,62]	Mild epigastric distress, nausea, and diarrhea.	Pregnancy and nursing. Should not be used by children.	A combination chondroitin/glucos-amine product contained manganese.[63]	Eight out of 25 products tested failed to contain indicated level of chondroitin.[64]	High doses may enhance effects of anticoagulant drugs.[65]
Chromium (Trivalent Chromium, Chromium Picolinate)	Weight Loss	Not effective for weight loss in healthy people.[66] Claims of performance enhancement, muscle building, and weight loss are unsubstantiated.[67]	Chronic active interstitial nephritis in humans.[68] There are concerns of picolinate causing DNA damage and reduced fertility based on animal studies.[69]	Pregnancy and nursing. Should not be used by children.[70]	Hexavalent chromium (CVI) has been identified in some chromium supplements. CVI is carcinogenic and causes ulcers, convulsions, kidney and liver damage, and death.[71]	The IOM estimates the safe and adequate daily intake to be 25mcg.	Use with insulin may increase risk of hypoglycemia.[72]
Comfrey (Symphytum officinale, Symphytum asperum, Symphytum x. uplandicum, beinwell, blackwort, bruisewort, slippery root, ass ear, wallwort, knitbone, black root, consolida, consound, gum plant, knitback)	Arthritis	There is insufficient reliable information to establish efficacy.[73]	Has been linked to chromosome damage, gastrointestinal lesions, pulmonary endothelial hyperplasia, and hepatic veno-occlusive disease, which can lead to cirrhosis[74] and death.[75]	Pregnancy and nursing.	Nine of 11 products tested contained pyrrolizidine alkaloids,76 which are toxic to humans.[77]	No reliable evidence.	Risk of toxicity when used with unsaturated pyrrolizidine alkaloid-containing herbs.[78]
Creatine (Creatine monohydrate)	Performance Enhancement	Studies indicate that creatine enhances anaerobic performance requiring brief, intense bursts of strength, but does not improve endurance, aerobic performance, or isometric strength.[79,80]	Weight gain, nausea, cramping, dehydration, incontinence, muscle strain, high blood pressure, diarrhea, dizziness,[81] acute renal failure,[82,83] and decreased renal function.[84,85,86]	Pregnancy and nursing. Renal disease/failure. Should not be used by children,[87] although used for children with muscular dystrophy and GAMT deficiency.[88]	Can be contaminated with creatinine (a waste product) or dicyandiamide.[89]	Doses usually exceed 20g per day.90 There is concern of impurities and higher or lower concentrations than those listed on the product label.[91]	Caffeine (guarana, kola nut) appears to interfere with any beneficial effects.[92] Linked to ischemic stroke when combined with ephedra.[93]
Dehydroepiandrosterone (DHEA)	Performance Enhancement	There is no credible evidence that DHEA can build lean muscle mass or enhance sexual performance.[94]	Male and female users may experience hepatotoxicity and increased risk of breast, prostate, and endometrial cancer.[95] Male users may experience testicular atrophy, aggressive tendencies, baldness, and high blood pressure. Female users may experience reproductive problems96 and masculinization, including hair loss and excessive hair growth.[97]	Pregnancy and nursing. Should not be used by children under age 18. Prostate, uterine, ovarian,[98] and breast cancer.[99]	No reliable evidence.	No reliable evidence.	Amplifies the effects of azidothymidine (AZT), zidovudine, barbiturates, cisplatin, prednisolone.[100]
Dong Quai (Chinese angelica, angelica sinensis, dang gui, tang-kuei)	Menopause	Not proven to be more effective then placebo.[101] There is no clinical evidence to support its effectiveness in the treatment or prevention of any medical condition.[102]	May be toxic. Can cause bleeding, photosensitivity,[103,104] and photodermatitis.[105]	Presents significant danger to pregnant women.[106]	No reliable evidence.	No reliable evidence.	Doubled prothrombin time and INR in a patient taking coumadin.[107] May increase risk of bleeding if combined with NSAIDs.[108]

† Study was based on subjective, self-reported answers to a questionnaire skewed towards efficacy and is therefore considered methodologically flawed.

Supplement	Indications	Efficacy	Side Effects	Contraindications	Contamination	Dosage & Purity	Concomitant
Echinacea (Echinacea angustifolia, E padilla, E purpurea, black sampson, purple coneflower, hedgehog, Indian head, snakeroot, red sunflower, scurvy root)	Cold Care	One study indicates echinacea is effective at relieving cold and flu symptoms faster than a placebo,[1109] others refute this claim.[110,111] It is not effective in treating upper respiratory infections in children.[112] A Cochrane review found insufficient evidence to recommend the use for treatment or prevention of common colds.[113]	Anaphylaxis, acute asthma, acute liver failure,[114] and erythema nodosum.[115] Long-term use may depress the immune system.[116]	Environmental allergies,[117] autoimmune disease,[118] diabetes, pending surgery,[119] pregnancy, and nursing.[120] Should not be used by children.[121]	Microbial contamination can occur during growing, harvesting, and production.[122] Some species may be confused with or adulterated with partheium integrifolium.	Samples purchased in retail stores often do not contain the labeled species.[123] Five of 19 products tested failed to meet standards of dosage and purity.[124]	May interfere with the anti-cancer chemotherapeutic effect of corticosteroids, may increase side effects of methotrexate, and decrease the effects of immuno-suppressant drugs.[125]
Ephedra (Ma huang, Ma Juang, ephedra sinica, ephedra intermedia, ephedra equisetina, ephedra shennungiana, cao mahuang, meertraubchen, ephedrine, epitonin, pseudoephedrine, Chinese joint-fir, country mallow, desert herb, brigham tea[126])	Weight Loss	One industry-supported study indicated a slight increase in metabolism but was inconclusive with regard to any contribution to weight loss.[127] May promote moderate weight loss, though more effective when combined with caffeine.[128,129,130] No evidence of long-term improvements in physical performance.	Mania,[131] psychosis,[132,133] sudden death,[134,135,136,137] stroke,[138,139,140] cardiomyopathy,[141,142] liver toxicity,[143] nervousness,[144] dizziness,[145] tremor, high blood pressure[146] and heart rate,[147] headache,[148] gastrointestinal distress, myocardial infarction,[149] hepatitis,[150] seizures,[151] tachyphylaxis, increased risk of ventricular atrial arrhythmia,[152] and addiction.[153] The [140] adverse events reported to the FDA between 6/1/97 and 3/31/99, included 17 reports of hypertension, 13 reports of palpitations and/or tachycardia, and 10 strokes. Ten events resulted in death and 13 events resulted in permanent disability.[154] Primate research indicates dopaminergic neuron damage similar to that caused by methamphetamine.[155]	Pregnancy, pending surgery,[156] anxiety, depression, narrow-angle glaucoma, coronary artery disease, cerebral circulatory impairment, psychiatric disorders, cardiovascular disease,[157] hypertension, thyroid disorders, diabetes.[158]	Has been adulterated with pharmaceutical-grade caffeine,[159] ephedrine hydrochloride,[160] and narcotics.[161]	Ephedra content varies within and among products.[162] Label claim is often below actual pill content.[163] There is no established, safe serving level or duration of use.[164] The ephedra industry and FDA disagree on the proper dosage.[165,166,167]	Co-administration with MAOIs can lead to life-threatening hypertension.[168] Concomitant ingestion of other botanicals and stimulants could affect the pharmacokinetic profile.[169] Also known to interfere with beta-blockers, methyldopa, theophylline, decongestants,[170] cardiac glycosides, guanethidine, halothane, and oxytocin.[171]
Folate (Folic acid)	Prenatal Care	Supplementing the diet significantly reduces the risk of neural tube defects.[172,173,174,175,176] May lower the risk of colon cancer.[177]	Long-term consumption of more than 5mg/day may have neurological effects. Very high doses of greater than 15mg per day can cause central nervous system and GI side effects.[178]	Vitamin B12 deficiency.[179]	No reliable evidence.	No reliable evidence.	May increase the activity of fluoxetine and alleviate the side effects of lometrexol and methotrexate.
Garlic (Allium sativum, aglio, ail, Dasuan, Knoblauch, La-juan, rustic treacle, stinking rose)	Cardiovascular Health	One meta-analysis indicates a small but significant antihypertensive effect.[180] Evidence of cholesterol reduction conflicts.[181,182,183]	Increased risk of postoperative bleeding,[184,185] heartburn, flatulence, sweating, lightheadedness, allergic reactions, and menorrhagia.[186,187]	Pregnancy and nursing; HIV/AIDS,[188] peptic ulcers,[189] pending surgery.[190] Allergy to plants in the Liliaceae family.[191]	No reliable evidence.	No reliable evidence.	Concomitant use with coumadin was followed by increased INR.[192] Reduces the blood concentration of saquinavir.[193,194]
Ginkgo (Ginkgo biloba, duck foot tree, icho, maidenhair tree, silver apricot)	Memory Enhancement	Conflicting evidence exists regarding enhancement of normal cognitive function.[195,196,197,198,199] Studies show it is effective in the treatment of dementia[200] and Alzheimer's disease.[201,202,203]	Long-term use has been associated with spontaneous bilateral subdural hematomas.[204] Case studies link ginkgo with cerebral bleeding[205] and epileptic seizure.[206]	Pregnancy and nursing.[207] Should not be used by children.[208] Hematologic disorders,[209] pending surgery,[210] epilepsy, seizures.[211] Should not be used by women trying to become pregnant.[212] Diabetes.[213]	Colchicine, a mitotic spindle poison, was identified as a contaminant in samples.[214]	25% of products tested failed to meet the potency standard.[215]	Patients taking coumadin or aspirin have experienced severe spontaneous bleeding after self-prescribing at the recommended dosage.[216,217] Can also intensify the effect of other anticoagulants,[218,219] and interfere with the action of NSAIDs.[220] May interact with certain diuretics[221] and trazadone.[222]

Supplement	Indications	Efficacy	Side Effects	Contraindications	Contamination	Dosage & Purity	Concomitant
Ginseng (Asian: Panax ginseng, allheilkraut, Chinese ginseng, Korean ginseng, ninjin, true ginseng. Siberian: Eleutherococcus senticosus, devil's shrub, eleuthero ginseng, Russian ginseng, wild pepper)	Diabetes, Immune Function	Effectiveness of Asian ginseng is not established beyond a reasonable doubt for any indication,[223] however, it has been shown to lower blood glucose levels.[224,225] Clinical trials have indicated Siberian ginseng has a small positive effect on cognitive performance.[226]	Hypertension, insomnia, nose bleeds, headache, nervousness, vomiting, and post menopausal vaginal bleeding are associated with overuse.	Hematologic disorders,[227] cardiovascular disease, hypertension, pregnancy, nursing, pending surgery,[228] and psychological imbalance. Not recommended for children.[229]	Has been contaminated with lead, quintozene pesticide, and hexachlorobenzene (a known carcinogen).[230]	Of 22 products tested, only nine met dosage and purity standards.[231]	Interactions with hypoglycemic drugs, NSAIDS, antiplatelet agents and MAOIs.[232,233] Patients who use Siberian ginseng may show falsely elevated digoxin levels.[234] May reduce the anticoagulant effect of warfarin.[235]
Glucosamine	Osteoarthritis	Meta-analyses confirm efficacy in the retardation[236,237] and treatment of osteoarthritis, especially in knee[238] and hip joints.[239]	Heartburn, epigastric distress, diarrhea.	Diabetes,[240] pregnancy, and nursing.[241]	A combination chondroitin/glucos-amine product contained manganese.[242]	Ten glucosamine-only products met ConsumerLab standards for dosage and purity.[243]	Some studies suggest it may increase insulin resistance.
Human Growth Hormone (Pituitary Hormone, hGH, recombinant human growth hormone)	Performance Enhancement	Studies indicate no athletic or sexual performance benefit from hGH.[244,245]	Dyspepsia, nausea, and diarrhea.[246] Increases the risk of leukemia in children.[247,248] Linked to colon cancer in adults that were treated with hGH as children.[249]	Active malignancy, pregnancy, nursing. Should not be used by children. Diabetes.	No reliable evidence.	No reliable evidence.	No reliable evidence.
Insulin-like Growth Factor (IGF-1, somatomedin)	Performance Enhancement	There is no credible evidence to support claims of promoting lean muscle mass or enhanced athletic and sexual performance.	High levels have been associated with elevated risk of prostate cancer.	Active malignancy and pregnancy. Should not be used by children.	No reliable evidence.	No reliable evidence.	No reliable evidence.
Kava (kava-kava, ava, ava pepper, kava pepper, kava root, kew, Piper methysticum, awa, Piper methysticum Forst. f., Piper methysticum G.Forst., sakau, tonga, wurzelstock, intoxicating pepper, kawa, kawa pepper, rauschpfeffer, yangona)	Anxiety	Analgesic, anticonvulsant, anesthetic, and neuroprotective properties proven only in animal studies.[250] Clinical studies have implied superiority of kava over placebo for the treatment of anxiety.[251,252,253]	Dermatomyositis, visual disturbances,[254] increased risk of suicide, dyskinesia, choreoathetosis, liver toxicity,[255] including hepatitis,[256,257] cirrhosis, and liver failure.[258,259] Gastrointestinal upset, dizziness, drowsiness, dry mouth.[260]	Should not be used by children. Depression, pregnancy, nursing, pending surgery.[261]	Lactone content of the root can vary; actual and labeled amounts of lactones also vary.	The quality of the extracts may vary between preparations.[262] The American Botanical Council discourages taking kava daily for more then four weeks.[263]	Interacts with barbiturates, antipsychotics, dopamine, and xanax.[264] Can produce a "high" and is often used as a recreational drug or aphrodisiac.[265] It is not recommended to take kava with alcohol.[266]
L-Glutamine	Attention Deficit Disorder (ADD/ ADHD).	Although there is no reliable evidence to support use in the treatment of ADHD, reports indicate it may improve concentration, alertness, memory, and recall.[267]	Constipation, bloating.	Pregnancy, nursing,[268] renal or hepatic failure.	No reliable evidence.	No reliable evidence.	Interacts with anticonvulsants,[269] lactulose,[270] hGH, indomethacin, methotrexate, paclitaxel.
PC-SPES	Prostate Cancer	Shown to lower prostate-specific antigen (PSA), serum testosterone, and inhibit the growth of prostate cancer cells.[271,272,273,274]	Gynecomastia, loss of libido, breast and nipple tenderness, venous thrombosis.[275]	Pregnancy and nursing.	Diethylstilbestrol (DES), indomethacin,[276] coumadin, xanax.[277]	No reliable evidence.	May confound the results of standard therapies.[278] May increase risk of bleeding when taken with anti-coagulants.

Supplement	Indications	Efficacy	Side Effects	Contraindications	Contamination	Dosage & Purity	Concomitant
Red Clover (Trifolium pratense, bee-bread, cow clover, meadow clover, purple clover, trefoil, trifoglio, wild clover)	Menopause	Although extracts have had estrogenic effects,[279] two randomized clinical trials have found no benefit over placebo for any menopausal symptoms.[280,281]	Breast tenderness, menstruation changes, weight gain.[282]	Infancy, pregnancy, and nursing.[283]	No reliable evidence.	Five of 18 products tested contained anywhere from 50-80% of the amount of isoflavones claimed on their label.[284]	May interfere with drug metabolism and interact with diabetic medications, pain relievers, ginkgo, and garlic.[285]
Saw Palmetto (Serenoa repens, cabbage palm, sabal, sabal serrulata, sagepalme, zwergsagepalme)	Benign Prostatic Hyperplasia	Can improve symptoms[286] including urinary flow[287,288,289] and excessive nighttime urination.[290,291] Effects are comparable to pharmaceutical therapies.[292,293,294,295]	Gastrointestinal complaints,[296] constipation, diarrhea, painful urination, decreased libido,[297] and erectile dysfunction.[298] May cause bleeding.[299]	Pregnancy and nursing.[300] There is one case report of intraoperative hemorrhage.[301]	One study reported a 97-140% difference in preparation compared with amounts stated on labels.[302]	The quality of commercial saw palmetto products varies widely.[303] Of 26 products tested, 35% failed to meet the standard potency of 85% sterol.[304]	Interacts with HRT and oral contraceptives.[305] May prolong bleeding time when used with antiplatelet or anticoagulant medications.[306]
St. John's wort (Hypericum perforatum, devil's scourge, goatweed, iperico, johanniskraut, klamath weed, millepertius, rosin rose, tipton weed, witch's herb, Nature's Prozac, Kira, Hypercalm, Psychotonin)	Depression	Studies indicate superiority to placebo in treating depressive disorders.‡[307,308] May increase brain metabolism in healthy subjects.309 Other studies indicate it is ineffective for the treatment of major depression.[310,311,312]	Diarrhea, nausea, anorgasmy, frequent urination, swelling,[313] abdominal discomfort, insomnia, headache,[314] rash, fatigue, restlessness, and photosensitivity.[315]	Pregnancy, nursing,[316] pending surgery.[317,318]	Five products tested contained twice the acceptable level of cadmium.[319]	Since the active constituents are not established, the whole extract must be consumed for a therapeutic effect.[320] Five of the 21 products tested contained less then amount claimed on the label.[321]	Interacts with drugs metabolized by the CYP monoxygenase enzyme system[322] and selective serotonin-reuptake inhibitors.[323,324] Compromises certain cancer drugs, potentially increasing patient's risk for cancer relapse.[325] Reduces plasma concentrations of digoxin, coumadin, phenprocoumon, oral contraceptives, irinotecan,[326] amitriptyline, cyclosporine,[327, 328] theophylline, and indinavir.[329,330,331]
Valerian (Valeriana officinalis, Valerianae radax, baldrianwurzel, phu, amantilla, baldrian, garden heliotrope, herbe au chats, setwall)	Anxiety, Insomnia	Evidence is inconclusive,[332] however three small, randomized clinical trials note improved sleep quality and decreased sleep latency.[333,334,335]	Allergic reaction, headache, restlessness, dilated pupils, cardiac disorders, dystonia, visual disturbances,[336] and liver damage.[337]	Pregnancy, nursing, hepatic impairment,[338] pending surgery.[339]	Products made from species other than valeriana officinalis may contain didrovaltrate, which is cytotoxic.[340]	Eight of 17 products tested failed to contain the expected or claimed amounts of valerenic acids.[341]	May increase bleeding and affect thyroid function.[342] May have an additive effect when taken with alcohol[343] may potentiate central nervous system depressants.[344]

‡ Both analyses included studies with significant methodological flaws, which undermines confidence in their results.

Appendix A: Commonly Used Dietary Supplements

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Appendix B: Selected Food & Drug Administration Enforcement Actions 1997 – 2004

Date	Product	Actual or Potential Adverse Event(s)	FDA Action(s)
February 18, 1997	Gamma Hydroxybutyric Acid (GHB)	Vomiting, dizziness, tremors and seizures; some deaths	Renewed 1991 warning against use
May 16, 1997	"Chomper" (digitalis derivatives)	Abnormal heart rate and rhythm, potential cardiac arrest	Issued warning against purchase and consumption
November 6, 1997	Herbal fen-phen	Shown to be not safe or effective and has been associated with "injuries"	Issued consumer warning
June 15, 1999	GHB, Gamma Butyrolactone (GBL), and 1,4 Butanediol (BD)	122 serious illnesses and 3 deaths	Issued an alert on misuse of consumer products
November 11,1999	Triax Metabolic Accelerator (triiodothyroacetic acid)	Contained a potent thyroid hormone which may cause serious health consequences including heart attacks and stroke	Issued a warning to consumers not to purchase or consume the product
February 10, 2000	St. John's wort	Drug interactions with Indinavir and other drugs	Issued warning to health professionals
June 1, 2000	Aristolochic acid	Kidney failure	Issued warning to health professionals
November 6, 2000	Phenylpropanolamine hydrochloride	Increased risk of hemorrhagic stroke in women; men may also be at risk	Issued a public health advisory which recommended that consumers not use any products that contain phenylpropanolamine
January 25, 2001	Neo Concept Aller Relief (contained aristolochic acid)	Aristolochic acid has been associated with kdieny failure and kidney cancer	Voluntary recall by manufacturer
June 7, 2001	Food and drink products containing "novel ingredients" including ginkgo biloba, Siberian ginseng and echinacea	"Little evidence" to show the herbs were "dangerous" and "scant proof" that they were safe	Sent letters to 3 food and drink manufacturers that put them "on notice" they may be required to submit evidence that their "ingredients are safe"
July 6, 2001	Comfrey, S. asperum (prickley comfrey), and S. x uplandicum (Russian comfrey)	Veno-occlusive disease (VOD) in animals; possible carcinogens	Issued letter to various organizations communicating concern about the marketing of dietary supplements containing these ingredients
August 6, 2001	Aristolochic acid	Nephropathy leading to end stage renal disease and urological malignancies	Issued consumer advisory and sent updated letters to industry and health professionals to communicate concern
November 19, 20, 2001	Lipokinetix (contained norephedrine, caffeine, yohimbine, diiodothyronine, and sodium usniate)	Liver injury or liver failure	Issued consumer warning to immediately stop use of the product; recommended that distributor remove product from market;
December 19, 2001	Kava (Piper methysticum)	Liver toxicity including hepatitis, cirrhosis, and liver failure	Informed healthcare professionals of adverse effects; requested healthcare professionals' assistance in reviewing cases of liver toxicity to determine if any may be related to the use of kava-containing dietary supplements
February 8, 2002 (updated September 20, 2002)	PC SPES, SPES	Contained undeclared prescription drug ingredients that could cause serious health effects if not taken under medical supervision	Issued consumer warning to stop use. Manufacturer voluntarily recalled PC SPES and SPES nationwide
March 25, 2002	Kava-containing dietary supplements	Liver-related injuries, including hepatitis, cirrhosis, and liver failure	Center for Food Safety and Applied Nutrition notified healthcare professionals and consumers of the potential risk of severe liver injury
July 3, 2002	Nettle capsules	Contained excessive amounts of lead; can lead to serious damage of the central nervous system, sometimes leading to permanent neurological damage	Nature's Way Products, Inc. recalled four lots of its 100-count Nettle capsules
August 13, 2002	Chaso (Jianfei) Diet Capsules and Chaso Genpi	May contain aristolochic acid leading to kidney toxicity; several people in Japan became ill and some died after having consumed these products	Alerted the public about these products because they posed a potential public health risk

Date	Product	Actual or Potential Adverse Event(s)	FDA Action(s)
October 7, 2002	Yellow Jackets (contain ephedra and other stimulants)	"Street drug alternatives" do not qualify as dietary supplements	Stopped imports of the product and informed operators of an Internet site selling Yellow Jackets that they broke the law
October 17, 2002	Kirkman's HypoAllergenic Taurine Capsules	Falsely claimed to treat autism	Ordered seizure of the dietary supplement which violated the Federal Food, Drug and Cosmetic Act
February 13, 2003	20 different dietary supplement products from Global Source Management and Consulting, Inc.	No adverse events reported, but products contained false and misleading labels	Requested U.S. Marshals seize products that were sold to consumers under the names Vitamin Hut and RX for Health
April 4, 2003	Vinarol tablets	Contained unlabeled sildenafil. Interaction between nitrates and sildenafil can result in profound and life-threatening lowering of blood pressure	Ultra Health Laboratories, Inc. and Bionate International, Inc. warned consumers not to purchase or consume the product
May 23, 2003	Viga Tablets (Best Life International)	Contained the unlabeled prescription drug ingredient, sildenafil. Interaction between nitrates and sildenafil can result in profound and life-threatening lowering of blood pressure	Best Life International warned consumers not to purchase or consume the product
June 17, 2003	Seasilver (Americaloe & Seasilver USA)	Fraudulent claims	As part of Operation cure.all, U.S. Marshals seize 132,000 bottles
June 20, 2003	Sigra, Stamina Rx, Stamina Rx for Women, Y-Y, Spontane ES and Uroprin (contained prescription strength tadalafil)	Interaction between nitrate-containing drugs and tadalafil can result in life-threatening lowering of blood pressure	Issued warning against use
June 24, 2003	Health Nutrition (RMA Labs) Viga or Viga for Women Tablets (contained unlabeled prescription strength sildenafil)	Interaction between nitrate-containing drugs and sildenafil can result in life-threatening lowering of blood pressure	Health Nutrition (RMA Labs) warned consumers not to purchase or consume the products
September 10, 2003	Star Anise Teas	40 reports of individuals, including about 15 infants, who became ill after consumption of product	Issued an advisory to consumers to avoid consumption of teas brewed from star anise
February 5, 2004	Betatrim, Thermbuterol, Stacker 2 (ephedra)	Unsubstantiated claims for the ephedra-containing products without adequate scientific basis	Announced seizure of supplements from Musclemaster.com in Northboro, MA
February 25, 2004	Green Hornet (ephedra)	Seizure, excessive heart rate, severe body rash and high blood pressure	Issued warning to consumers not to purchase or consume product
March 26, 2004	Solutions IE Ageless Formula II (contained significantly higher-than-labeled level of vitamin D3)	May result in abnormally high blood levels of calcium and urea	Aloe Commodities International, Inc. recalled 1600 bottles of product. FDA urged consumers of affected lots to stop taking them immediately
April 9, 2004	Trip2Night, Invigorate II, Snuffadelic, Liquid Speed, Solar Water, Orange Butterfly, Schoomz, and Green Hornet Liquid (contained controlled substances GBL and GHB; ephedra; and over-the-counter drugs diphenhydramine and dextromethorphan)	"Street drug alternatives" are misbranded drugs, and do not qualify as dietary supplements	Issued warning to consumers not to purchase or consume products
November 2, 2004	Actra-RX or Yilishen (contained prescription-strength quantities of sildenafil)	Interaction between sildenalfil and other prescription drugs may cause drop in blood pressure	Issued warning to consumers not to purchase or consume products
December 16, 2004	FCC Products, Inc. Ginseng (contained pesticide chemical residues procymidone and quintozene)	No tolerance established for residues of procymidone and quintozene in ginseng	Initiated seizure of product by U.S. Marshals

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