

*Sounding Board***BOTANICAL MEDICINES —
THE NEED FOR NEW REGULATIONS**

IN 2001, \$17.8 billion was spent in the United States on dietary supplements, \$4.2 billion of it for herbs and other botanical remedies.¹ The popularity of these products has increased over the past decade, probably stimulated by sharp increases in prices of prescription drugs, restricted access to physicians imposed by managed care, media reports of adverse effects of prescription drugs, and, most important, the enactment in 1994 of the Dietary Supplement and Health Education Act (DSHEA). By broadly defining herbs and other botanicals as “dietary supplements,” the DSHEA substantially altered the definitions, standards, and mechanisms under which claims about the effectiveness and safety of these products are evaluated and enforced.² This classification, which we believe to be inappropriate, has resulted in a serious and growing public health problem. In this article, we summarize problems inherent in the manufacture, analysis, and post-marketing surveillance of botanical medicines and propose new legislative regulations to address these issues. Such legislation would increase governmental oversight and manufacturers’ responsibility for ensuring the safety of consumers at the high level citizens have come to expect.

The perception that botanical products used as folk remedies are inherently safe is based on traditional use rather than on systematic studies designed to detect adverse effects. Nevertheless, evidence of the toxicity of such products has accumulated.³⁻¹⁰ This is not surprising, since botanicals are complex mixtures of chemicals, described by Robbers and Tyler as “crude drugs of vegetable origin,”¹¹ many of which are potentially toxic. In the past year alone, the Food and Drug Administration (FDA) was compelled to issue warnings about nephrotoxic, hepatotoxic, and carcinogenic effects associated with botanical products containing kava, comfrey, and aristolochic acid — all herbal remedies used widely in the United States and Europe.⁵ Other factors influence efforts to ensure the safety of botanical products; several issues are discussed below.

LACK OF STANDARDIZATION

Consistency in composition and biologic activity are essential requirements for the safe and effective use of therapeutic agents. However, botanical preparations rarely meet this standard, as a result of problems in identifying plants, genetic variability, variable growing conditions, differences in harvesting procedures and

processing of extracts, and above all, the lack of information about active pharmacologic principles. The use of chromatographic techniques and marker compounds to standardize herbal preparations promotes batch-to-batch consistency but does not ensure consistent pharmacologic activity or stability. Moreover, analyses of purportedly standardized herbal preparations reveal that botanical products often do not contain the amount of the compound stated on the label.^{12,13} “Their potency may vary and their purity is suspect,” warns the *Medical Letter*.³

**ADULTERATION OF BOTANICAL
PREPARATIONS**

Many herbal products contain undisclosed prescription or over-the-counter drugs and heavy metals.¹⁴⁻¹⁷ In 1998, the California Department of Health reported that 32 percent of Asian patent medicines sold in that state contained undeclared pharmaceuticals or heavy metals.¹⁵ The drugs most frequently found were ephedrine, chlorpheniramine, methyltestosterone, and phenacetin; 10 to 15 percent contained lead, mercury, or arsenic. Subsequently, more than 500 Chinese patent medicines were screened for the presence of heavy metals and 134 drugs.¹⁶ Approximately 10 percent were found to contain undeclared drugs or toxic levels of metals. The FDA and other investigators¹⁷ have also reported the presence of prescription drugs, including glyburide, sildenafil, colchicine, adrenal steroids, alprazolam, phenylbutazone, and fenfluramine, in products claiming to contain only natural ingredients. For example, PC-SPES is a patented herbal preparation marketed to “enhance prostate health,” but commonly used to treat prostate cancer. Reports of its effectiveness have appeared in major medical journals.^{18,19} After chemical analysis of PC-SPES revealed the presence of diethylstilbestrol, indomethacin, warfarin, or a combination of these drugs,¹⁸ the product was removed from the market.

Recently, the Japanese Ministry of Health, Labor, and Welfare reported that the use of certain imported Chinese dietary supplements was associated with hepatic failure and hyperthyroidism.²⁰ These products proved to be adulterated with *N*-nitroso-fenfluramine, fenfluramine, and thyroid extracts. As of September 20, 2002, a total of 622 patients were known to have become ill, with 148 requiring hospitalization; 3 deaths have occurred.²¹ The offending products were recalled, and the ministry will now require manufacturers to perform chemical analyses on all imported dietary supplements.

**INTERACTIONS BETWEEN HERBS
AND DRUGS**

Botanical medicines can act through a variety of mechanisms to alter the pharmacokinetic profile of

concomitantly administered drugs.²² St. John's wort, for example, induces the cytochrome P-450 isozyme CYP3A4 and intestinal P-glycoprotein, accelerating the metabolic degradation of many drugs, including cyclosporine, antiretroviral agents, digoxin, and warfarin.²³ Serious adverse effects have been reported when the addition of St. John's wort caused serum levels of cyclosporine and antiretroviral agents to fall to sub-therapeutic levels.

The extent of herb-drug interactions is unclear, but the potential magnitude of this problem is suggested by a recent survey of medication use in the United States.²⁴ Among persons over the age of 18 years, 50 percent said they had taken at least one prescription drug during the preceding week. Among women 65 years or older, 23 percent had taken at least five prescription drugs. Moreover, 16 percent of persons taking prescription drugs also took an herbal or supplement preparation. Thus, many people in the United States unknowingly risk therapeutic failure or adverse effects caused by herb-drug interactions; this is especially true of older people who take multiple medications for chronic diseases.

LACK OF REPORTING OF ADVERSE EVENTS

The FDA maintains surveillance of prescription drugs by requiring prompt reports from manufacturers of all adverse effects brought to their attention. Nevertheless, it is estimated that only 10 percent of serious adverse effects associated with the use of prescription drugs are ultimately reported to the FDA.²⁵ Pre-marketing safety testing is not required for dietary supplements, and there is no mandatory requirement for manufacturers of supplements to record, investigate, or forward to the FDA reports of adverse effects they might receive. Although some adverse reactions to botanical medicines are acute and symptomatic, others, such as renal failure and cancer, have a delayed and gradual onset. Furthermore, the relation of the prior consumption of an herbal remedy to a medical problem with delayed onset may not be readily apparent.

The lack of reporting of adverse events to the FDA has generated concern at the level of the federal Office of the Inspector General.²⁵ In 2001, the FDA received approximately 500 reports of adverse events related to dietary supplements, and poison-control centers in the United States received 19,468 reports.²⁶ up from 6914 in 1998. In addition, the FDA is often unable to investigate the reports it does receive, either because the consumer's identity and address cannot be obtained or because the ingredients in the supplement and the identity and address of the manufacturer are unknown. The Inspector General's report²⁵ estimates that less than 1 percent of adverse events

caused by dietary supplements, including herbs, are reported to FDA. Only a fraction of these are adequately investigated.

CURRENT REGULATION OF BOTANICAL MEDICINES

Regulation of food and drugs has always been strongly resisted by industry, and Congress has acted in this case only in response to strong pressure from the public. The Food and Drug Acts passed in the 20th century, which provided important protection to the public, were subverted by the passage of the DSHEA. This misguided legislation freed the dietary supplement industry from effective oversight by the FDA, transferring the burden of proof for establishing the safety of herbal medicines from the manufacturer to the FDA. Dietary supplements are now subject to lower safety standards than food additives. Consumers are provided with more information about the composition and nutritional value of a loaf of bread than about the ingredients and potential hazards of botanical medicines.

The way in which the restrictions imposed by the DSHEA hinder the FDA from promptly removing dangerous products from the market is illustrated by the problems posed by the herbal supplement ephedra. Ephedrine alkaloids are present in many supplements marketed to induce weight loss and to boost energy. Like their chemical relative methamphetamine, or "speed," these preparations act as powerful stimulants to both the cardiovascular and the central nervous systems, and their use has been associated with strokes, cardiac arrhythmias, seizures, acute psychosis, myocardial infarction, and death.^{27,28} More than 1200 serious reactions related to ephedra have been reported to the FDA, though the actual number of events is undoubtedly far greater. An estimated 12 million people in the United States take Metabolife 356, a product containing ephedra, caffeine, and several herbs. It was recently revealed that 13,000 complaints have been registered with the manufacturer. Included were reports of several hundred people who required hospitalization and 80 incidents of serious injury or death.²⁹ Under current regulations there is no penalty for withholding reports of adverse effects. However, the Justice Department, at the FDA's request, has initiated a criminal investigation because of false statements that claim an absence of adverse effects. Canadian — but not U.S. — health authorities have requested the voluntary recall of health products containing ephedra, noting its enhanced toxicity when combined with caffeine.³⁰

THE NEED FOR NEW REGULATIONS

Public awareness of the hazards of dietary supplements has increased in recent years, and a majority of

the U.S. public supports the idea of new rules that would require the FDA to review the safety of new dietary supplements before their sale; that would give increased authority to the FDA to remove unsafe products from the market; and that would regulate advertising claims about the health benefits of dietary supplements.³¹ However, for the FDA to be effective in carrying out such a mandate, new legislation and resources are required. We believe that six legislative proposals, outlined below, could accomplish this goal without denying consumers access to a popular class of products.

First, the address and telephone numbers of all companies, as well as the names of the responsible persons, involved in manufacturing dietary supplements for sale in the United States should be registered with the FDA. The FDA is currently severely hampered in its efforts to investigate the adverse effects of dietary supplements by the lack of information about manufacturers and distributors.

Second, the manufacturers of dietary supplements should provide evidence of good manufacturing practices, and the FDA should be given the authority to inspect manufacturers' records. In 1999, the FDA held public meetings and published an advance notice of a proposed rule that addresses this issue. Though the announcement of a proposed rule is said to be imminent, the botanical industry has consistently blocked such a proposal. The extension of good manufacturing practices to manufacturers of herbal products would go far toward preventing adulteration and improving the standardization of marketed botanical products.

Third, the manufacturers of dietary supplements should obtain premarketing approval from the FDA by demonstrating that their products present no substantial or unreasonable risk of injury under conditions of recommended use, as suggested on the label. Manufacturers of supplements should assume and bear full responsibility for ensuring the safety of their products, including paying the relatively low costs of conducting appropriate testing, as is required for prescription and over-the-counter drugs.

Fourth, the manufacturers of dietary supplements should be required to report all adverse effects promptly to the FDA. This essential element of post-marketing surveillance is required for all prescription drugs and some over-the-counter drugs.

Fifth, the labels of dietary supplements should contain a list of constituents that unambiguously identifies herbs by their botanical and common names. Information about possible adverse effects, including the potential for herb-drug interactions, should be included.

Sixth, the Department of Health and Human Services should organize expert panels to review the

safety of all dietary supplements, except for essential nutrients and single-vitamin and multivitamin preparations. This process should be modeled after the National Academy of Sciences Drug Efficacy Study, which completed the complex task of evaluating the safety and efficacy of 4000 drugs in just three years.

CONCLUSIONS

The medical community has been slow to respond to the public health issues and educational problems resulting from the weakened regulation of dietary supplements. However, the numerous reports of adverse effects and deaths associated with botanical health products, the distribution and widespread sale of adulterated products, and the marked increase in misleading promotional claims on the Internet demand prompt action to protect the public health. The European Parliament is currently considering measures to ensure that all traditional herbal medicinal products used in member countries have demonstrated efficacy and an acceptable level of safety.³² The legislative reforms we propose here are likely to be opposed by powerful political and economic forces^{2,33} and by many proponents of complementary and alternative medicine. For this reason, vigorous and concerted action is needed to educate the public and Congress about the critical need for new regulatory safeguards and for the government funding to implement them.

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