

Ephedra-Based Dietary Supplement Products and Issues For Product Sellers

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This article is adapted from a presentation made by the author to the Pharmacy Liability Sub-Committee of the Medical Liability Committee of the Defense Research Institute in March 2003.

Introduction

Brewing over the past several years has been the possibility of a significant amount of litigation involving nutritional supplements. These products include ephedra, or Ma Huang, which was recently the focus of intense media attention following the death of a professional baseball player during spring training. The death occurred under circumstances that led people to believe that the athlete's use of an ephedra-based weight-loss product contributed to his death. This newsworthy incident renewed ongoing requests that ephedra products be banned from the market, or at a minimum, that they be subject to FDA regulation. There have been calls for congressional action to ban these products, and regional governments such as Suffolk County in New York have passed legislation banning the sale of such products locally.

A political firestorm such as presently exists for ephedra products will inevitably lead to increased litigation involving the manufacturers and purveyors of the products, as well as nutritionists, personal trainers, and physicians or alternative medicine practitioners who may recommend or provide them.

The following commentary will provide an overview of the product, the regulatory scheme, some current developments, and some recommendations regarding the defense of suppliers of these products who may be the subject of litigation. This is not intended to be a comprehensive historical, legal, or scientific discussion of ephedra litigation.

What is Ephedra?

Ma Huang is a Chinese plant whose extract has been used for medicinal purposes, according to reports, for upwards of 5,000 years. Many of its supporters have touted its longevity of use as proof of its safety. This type of logic may be questionable.

Ephedra is an extract of the Ma Huang plant, and it has been used for

millennia in China for its respiratory benefits in the treatment of hay fever and asthma. The Indo-Aryan society ate the plant to give strength and happiness, and to combat exhaustion. Though it is reported that the Romans used ephedra, it was not widely used in Europe after Roman times.

In the 1970s, a Danish physician treating asthmatics with an ephedrine compound serendipitously found that his patients experienced weight loss. Subsequent studies by obesity researchers demonstrated significant weight loss when ephedra was combined with caffeine, as compared to placebo.

Through the current time, ephedra-based products are touted as being good for weight loss, energy enhancement, muscle growth, and a host of other beneficial results, including

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sexual enhancement. However, since the early 1990s, the FDA has been in receipt of reports of side effects, including heart attacks, strokes, and psychoses associated with the ingestion of ephedra products.

Ephedra is big business, with sales of ephedra-based products in 2002 reaching \$1.24 billion. Although this figure was down 14% from 2001, likely due to the rash of poor publicity, it shows that a lot of product is sold every year. The ephedra product category has been increasing in volume as well. American Health Line (1), cites 424 million doses sold in 1995, followed by an increase to 3 billion in 1999. A recent survey of 14,000 United States adults indicated that 1% of them had used an ephedra-based product in the previous two years. (2)

Regulatory Background

Products that contain ephedra are considered to be nutritional supplements, not drugs. For years it was unclear whether the FDA had the authority to regulate nutritional supplement products such as products containing ephedra. The FDA's ability to regulate drugs and food has been unchallenged. Logically, it would seem that the FDA ought to be able to regulate products marketed as having health benefits, like ephedra products. However, that is not our regulatory scheme.

Before being able to sell a drug for a specific use, a drug manufacturer must be able to demonstrate to the FDA that the drug is safe for that intended use. In general, the manufacturer must also demonstrate to the FDA that the drug's labeling is accurate and complete.

Congress, however, created a different and much less stringent regulatory framework for nutritional supplements (like ephedra-containing products). In 1994, Congress passed the Dietary Supplement Health & Education Act (DSHEA). Basically, the manufacturer of a nutritional supplement product complies with DSHEA by positioning its product in such a way that it makes no claims that the product will treat specific diseases, and by adding label statements that the FDA has not studied or approved the product, and that the product is not "intended to diagnose, treat, cure or prevent any disease." Pick up almost any popular magazine, walk down the aisles of the pharmacy sections of large supermarkets,

chain drug stores or health food stores, or even a local health club, and you will see ads for ephedra products and product labeling that fits within this broad regulatory framework.

From its enactment, the DSHEA has been subjected to significant criticism, and the FDA has chafed against its restrictions. Particularly for ephedra products, the FDA has been vocal in its criticisms. In 1997, the FDA made it clear through proposed regulations (3), which never went into effect, that it wanted to regulate the ephedra market via labeling that limited 'serving' size, limited recommended daily consumption, and limited the length of time that the product should be taken. In addition, labeling was requested to warn against the use of ephedra-based products during pregnancy and in other health conditions, and to caution against its use with certain products such as caffeine. At the time that these regulations were proposed, the FDA found on the market some 125 ephedra-based dietary supplement products, which were being marketed for uses such as weight loss, body building, increased energy, improved mental concentration, increased sexual sensations or euphoria, or as alternatives to illicit street drugs.

From 1993 to 1997, the FDA received more than 800 reports of side effects (Adverse Event Reports - AERs), associated with more than 100 different ephedra-based dietary supplements.(4) The FDA reviewed the AERs and concluded that the most common complaints were of symptoms that were consistent with the known pharmacologic and physiologic effects of ephedra. The FDA felt that even in the absence of a case-controlled study demonstrating causation in a statistical manner, the nature of the reviewed evidence demonstrated causation to the FDA's satisfaction.

Nonetheless, the General Accounting Office issued a report in 1999 which concluded that the FDA did not have sufficient scientific evidence to support the regulations that it wished to promulgate. (5)

In June 2002, President Bush, to some criticism, directed a complete review of the issue of whether ephedra-based dietary supplements should be banned. The review was to be done by the Rand Corporation and subsequently evaluated by the National Institutes of Health to determine if additional study was necessary. (6)

In February of 2003, a New York Congressman announced plans to introduce legislation that would allow the FDA to regulate ephedra.

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State and local governments have already acted to regulate and limit the sale of ephedra-containing products. Nassau County, New York, banned ephedra products except for weight loss and body building purposes. The New York State Department of Health banned twenty specific ephedrine products being marketed as street drug alternatives. Florida banned all non-medicinal uses of ephedrine. Tennessee and Louisiana restricted ephedrine to prescription use only, with some exceptions. Ohio requires that a licensed pharmacist dispense ephedrine products and that purchasers be at least 18 years old; cold and flu ephedrine products are excepted. (7)

Current Events

The NCAA, National Football League, and the International Olympic Committee prohibit the use of ephedra-containing products. Major League Baseball does not ban the product, with its players' union arguing that legally available products should not be denied to baseball players. The American Medical Association in October 2002 made clear its position that ephedra-containing diet products should be removed from the marketplace because the risk-benefit ratio for those products was felt to be unacceptable. Canada issued an advisory to its citizens not to use products containing ephedra or ephedrine.

By February 2000, the FDA had received 1,398 reports of adverse events associated with ephedra, with 81 deaths and 32 heart attacks. (8). In the wake of the baseball player's death in 2003, The FDA is contemplating further action as to ephedra products. (9).

In November 2000, the New England Journal of Medicine released on its web site, not waiting for subsequent publication of the article, the results of a study showing that out of 140 reports of serious problems with ephedra-containing products, 87 cases were definitely, probably, or possibly linked to ephedra products. In the published article, the authors concluded, "The use of dietary supplements that contain ephedra alkaloids may pose a health risk to some persons. These findings indicate the need for a better understanding of individual susceptibility to the adverse effects of such dietary supplements." (10)

As of 2003, the FDA has received reports of nearly 100 deaths reportedly associated with ephedra products. (11) A 2003 article arising out of the Hemorrhagic Stroke Project at the University of Texas (12) concludes that ephedra was not implicated in increased risk of hemorrhagic stroke, except perhaps at higher doses than recommended. An article in the March 2003 *Annals of Internal Medicine* (13) reports that the United States Poison Control Centers recorded 1,178 adverse reactions to ephedra products in 2001. (14). Of course, demonstration of association is not proof of actual medical causation.

In 2002, the United States Attorney General announced a criminal investigation of Metabolife, an ephedra product manufacturer, in regard to statements by the company president denying awareness that its products had caused significant side effects. The government alleged that the statement was false and the company had received thousands of complaints of side effects. The company's position was that the statement was, and is, true – that its products have never been proved to cause significant side effects.

In 2002, one company admitted receiving almost 14,000 adverse event reports since 1995 concerning ephedra, but disputed causation between the reported events and the ephedra product. (15). In November 2002, an Alabama jury awarded \$4.1 million to four people who suffered strokes or heart attacks after taking an ephedra-based appetite suppressant. (16). In January 2003, a federal district court judge in Ohio allowed a proposed class action to survive a motion to strike class action allegations. Some parts of the complaint were dismissed, but others were allowed to stand, at least at a preliminary stage. Of note, product sellers and suppliers are defendants in that suit. Metabolife presently faces more than 100 suits alleging personal injury involving its products. (17).

The manufacturers maintain that the products are safe when used in accordance with their labeling. They take the position that nearly 30 studies show no adverse events and limited side effects from ephedra-based drugs. (18).

However, manufacturers have been feeling the legal and market pressures against ephedra and have been responding. In November 2002, Twinlab Corporation announced plans to switch to non-ephedra supplements by 3/31/03. Also in November 2002, General Nutrition Centers stopped selling ephedra products to minors. In January 2003, EAS, a manufacturer of ephedra products, chose to halt production of the products. Also in January 2003, 7-Eleven directed its franchisees to remove ephedra products from its shelves. (19).

Legal Issues

A comprehensive discussion of the legal issues to be faced by potential defendants is beyond the scope of this article. Anyone representing pharmacies or suppliers of these products should consider the following issues while developing the legal defenses in each case:

- ✓ Proximate cause - general causation and specific causation - must be completely evaluated by obtaining the pertinent medical literature, medical records, and reviews by appropriate experts.
- ✓ Consider the relationship between the seller and the customer in the individual client's case. Is there

something more than the plaintiff simply walking into the store, picking up a product from the shelf, and buying it? Was there interaction and discussion between the plaintiff and the store's employees? Was the plaintiff steered to a particular product? Was there a discussion about other supplements or medications that the plaintiff was taking?

- ✓ Did the supplier recommend literature to the plaintiff to assist the plaintiff in making decisions?
- ✓ In circumstances where the store is providing counsel and advice to its customers, what training and quality control exist in regard to what the employee tells the customers?
- ✓ What manufacturer's advertising is placed in the store or in the marketplace by the supplier, and why is that advertising chosen over some other advertising?
- ✓ Does the store make its own written materials available for customers considering different products to assist them in making choices between products? Do the sales people assist the customer in making choices between products?
- ✓ The liability issue may boil down to whether the client's operation is the type in which there is no store input regarding the customer's choice of product or the type in which the client provides significant input into the customer's choice of product: The more client input for customer decisions, the greater the likelihood of liability independent from that of the manufacturers.
- ✓ Be aware that there may or may not be the same type of cooperation between retailers and manufacturers that is customary in other pharmaceutical litigations. The lawyer representing the company that manufactured the product purportedly taken by the deceased baseball player stated: "It is difficult for us to reach out into the marketplace and control what retailers do. We strongly recommend that all consumers read and follow the label instructions prior to use." *New York Times*, 2/23/03, Section 14 *Westchester Weekly*, page 5. (20)
- ✓ Does state law permit the sale of such products over the counter? Was the product in question among those appropriate to be sold in this state?
- ✓ Does the client advertise these products, and if so, what do the advertisements say? Analyze how the advertisements will affect defense issues.
- ✓ What is the client's relationship with the manufacturer? Can the manufacturer be persuaded to assume the client's defense? Are there independent claims being made against the client that prevent an assumption of the defense?
- ✓ Are there contracts between the client and the manufacturer?

Ironic Questions

Cytodyne, a manufacturer of one of the leading ephedra-based products, touts an appetite suppressant on its web site (and similarly in print ads) as follows: "Best of all, it works without containing ephedrine." To quote a journalist on this issue, "If ephedra is so good to avoid, why sell it at all?" (21)

With chain stores filled with branded products such as CVS toothpaste, or Duane Reed aspirin, or Eckerd's ibuprofen, why do we not see the chain stores branding ephedra products? As with the first ironic question, a journalist must be credited for raising this question. (22)

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LMI on the Move

Elizabeth B. Juliano, President, Litigation Management, Inc. will be moderating a session titled "Successful Practice Development — Getting Started, Staying the Course, and Finishing Strong" at the ABA Women in Product Liability Conference in Atlanta on November 6, 2003. Panelists include:

- Beth Kaufman, Esq. - Schoeman, Updike & Kaufman, LLP
- Alfred T. Romanoski - Law Firm Marketing Consultant, Alfred P. Romanoski, Inc.
- Chilton Davis Varner, Esq. - King & Spalding, LLP

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HERBAL MEDICINE

Spicing Up Litigation

By Cindy Pordon, DO, and Erin Rooney, RD, Litigation Management, Inc.

Despite signs of slowing sales and recent negative media coverage of the 18-billion-dollar (1) dietary supplement industry, it is expected that consumer demand for supplements will continue and the industry will likely grow.⁽²⁾ The Food and Drug Administration estimates that there are currently more than 29,000 varieties of herbal and dietary supplements available to consumers, with more than 1,000 new products introduced each year.⁽³⁾ Health professionals need to keep this in mind when evaluating and treating patients. In addition, attorneys need to consider this when reviewing cases to determine if supplements may have been a factor in an alleged injury.

A survey published in *The Journal of the American Medical Association* in January of 2002 showed that there was a significant overlap in the use of prescription medications and herbals/supplements by adults in the United States.⁽⁴⁾ Health experts are realizing that Americans love to self-medicate. David W. Kaufman, ScD, lead author of the study, noted that health care providers need to be aware that a substantial number of people are taking herbal preparations as well as prescription drugs, and the possible interactions of these products have not been well studied.⁽⁴⁾ Herbal supplements appeal to consumers for a wide variety of reasons. They expect that these products will make them feel better, prevent illness, prolong life, build strength and muscle, and aid

weight management; consumers may also be using supplements on the advice of a physician.⁽⁵⁾ The heaviest users of supplements are baby-boomers age 46 and older, hoping to alleviate or avoid the effects of aging. Despite the widespread use of supplements, many Americans may not be well equipped to make informed choices about their responsible use. More information is needed by consumers regarding how supplements work in the body, what dosages are recommended, and warnings of potential adverse reactions. Consumers may not be careful about dosages, often assuming that more is better. In addition, while 92% of consumers said they consult their doctors about prescriptions, only 49% discuss supplement use with their doctors, and consumers over age 65 are the least likely group to discuss supplement use with their doctor.⁽⁶⁾

In illustration, consider the following hypothetical case study as reviewed by a medical/legal analyst who suspected that a patient might have been combining herbal remedies and prescription drugs. The discussion also focuses on Food and Drug Administration actions in regard to dietary supplements.

Case Study: Medical Issues

Jane Smith, age 54, alleges that she suffered a stroke as the result of taking a common prescription medication. As one of her treating physicians attested, she presented quite a challenge with respect to managing her multiple medical problems. She was a smoker, despite multiple recommendations to quit. Her medical history included adult-onset diabetes, hypertension, and paroxysmal atrial fibrillation [heart rhythm abnormality that can result in blood clots]. She had been non-compliant with traditional therapies that had been

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prescribed in the past. In reviewing records from other physicians, the medical analyst noticed that she seemed to prefer a “natural” approach. She took many supplements, frequently following the advice of friends who would recommend various remedies that “worked for them.” The names of these supplements were not specified in the physician office notes. The anticoagulant warfarin had been prescribed because of the potential risk of stroke due to her atrial fibrillation. Adjusting the warfarin dosage was difficult, and marked fluctuations in the Prothrombin Time [PT] levels persisted.

Approximately 8 months after starting warfarin, Ms. Smith was admitted with a hemorrhagic stroke. She had a prolonged hospitalization, and was left with impaired right arm function, difficulty swallowing, and memory loss, all of which contributed in her inability to return to her previous occupation as a computer programmer. Her treatment included intensive physical and occupational rehabilitation. A nutrition consultation was also obtained to help identify any dietary indiscretion that may have been contributing to the PT level fluctuations.

Case Study: Review of the Records

All references to traditional forms of treatment, as well as all references to complementary or alternative therapies were scrutinized in Mrs. Smith’s records. Information is often “hidden” in records other than physician notes. Patients frequently do not report the use of supplements to their physicians and physicians do not always ask specifically for this information, erroneously assuming that patients will include these products when questioned about their current medications. The general public often does not view supplements as medications. Therefore, this information may not be readily identified in review of physician records. Information regarding the use of supplements can often be found in dietary, physical and occupational therapy, chiropractic, nursing, social service, and psychiatric records. Dietary records may also indicate the use of some food prod-

ucts, such as tea, which may contain herbal additives. Key phrases may include references to nutritional supplements, vitamins, or natural products. It is also important to note if the patient engages in alternative practices [such as acupuncture], participates heavily in sports or weight loss, or belongs to a fitness facility as these may indicate an interest in or use of supplements. It is important to remember that laymen may refer to supplements with different nomenclature. Physicians and attorneys should phrase an inquiry about supplements using descriptive terms such as herbal products, nonprescription medications, dietary aids, home remedies, and over-the-counter preparations.

In Ms. Smith’s case, the nutrition assessment revealed that in addition to enjoying a salad almost every day, she was taking vitamins and supplements. Further questioning revealed that she was taking vitamins A, C, and E, ginkgo biloba, and another herbal remedy to enhance well-being.

The dietician requested that her family members provide the actual supplement bottles in order to assess the ingredients. Upon review, it was noted that one product contained multiple herbs, including ginseng. The label directions for this herbal supplement recommended taking two pills per day with food. Ms. Smith admitted to taking four to six pills daily, since her neighbor “felt so

much better at that dose.”

Reviews of laboratory records that may be beneficial in the analysis of Ms. Smith’s case include coagulation and liver function studies¹ [Tables 1a and 1b]. Trending of these test results, especially noting abnormalities prior to the use of the medication in question, may give insight into alternative causation. PT and INR² levels may be difficult to “adjust” in patients taking warfarin. It is important to note that dietary changes [Table 2] and many traditional medications, as well as supplements [Table 4], may affect the action of warfarin. These may either potentiate or “inactivate” warfarin, resulting in either prolongation or normalization of the PT and INR. Abnormalities in liver function tests may indicate prior or current underlying liver disease. Other prescription or over-the-counter medications may alter liver function. Elevations of liver function tests, in conjunction with the use of warfarin, may result in prolongation of the PT and elevation of the INR, thus predisposing the patient to increased bleeding problems, either spontaneously or as the result of injury.

Physicians and attorneys should phrase an inquiry about supplements using descriptive terms such as herbal products, nonprescription medications, dietary aids, home remedies, and over-the-counter preparations.

¹ Severe liver dysfunction leads to failure of protein synthesis resulting in prolonged clotting times and bleeding.

² INR (international normalized ratio) is used in monitoring of patients taking warfarin. It is applied to the results of the PT (prothrombin time) to adjust for the different conditions in labs performing the test.

³ Green leafy vegetables contain high levels of Vitamin K, which counteracts the anticoagulant effect of warfarin.

Case Study Analysis

There are multiple inherent difficulties in warfarin management. Often, dietary changes such as periodic increased consumption of salads³ will affect PT levels and may require changes in warfarin dosing. Hemorrhagic stroke may be caused by the potentiation of warfarin's blood thinning properties by the use of ginkgo and ginseng. Although not specific to Ms. Smith's case, head injuries, accelerated hypertension, and congenital abnormalities such as arteriovenous malformation would also warrant consideration as possible etiologies for hemorrhagic strokes. In the case of Ms. Smith, it was identified that outpatient records alluded to the use of supplements. Further investigation of hospital records, including all nursing and ancillary notes, identified the self-administration of ginkgo biloba for memory enhancement, and a product that contained ginseng to improve her "energy level." This information was identified in the nutrition consult.

General Issues

The use of herbal supplements is a time-honored, worldwide practice. Recently, the general public's interest in com-

plementary and alternative medicine [CAM] has been increasing. People are drawn to herbal supplements for many reasons. Some individuals feel they are "safer," because they consider them to be "natural." Many people are unaware of the potential side effects that may occur with their use. The National Center for Complementary and Alternative Medicine [NCCAM] was established in 1998 at the National Institutes of Health. NCCAM defines CAM as including a diverse group of medical and health care practices and products that are not currently considered conventional medicine. Complementary medicine is practiced in conjunction with conventional medicine; alternative medicine is practiced in place of conventional medicine. Integrative medicine combines mainstream medical therapies and CAM therapies for which some scientific evidence exists regarding safety and effectiveness. Dietary supplements are considered to be a type of CAM therapy.⁽⁷⁾ The Dietary Supplement Health and Education Act of 1994 has defined this wide of array of products.⁽⁸⁾

Although approximately 30% of traditional medicines are derived from botanicals, we know little about the true benefits and risks of herbal therapies. Most physicians are un-

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"I've thrown in some prescription drugs that don't interact well."

familiar with supplements.(9) This may be another reason why many medical records lack documentation of supplement use. Although specific guidelines have not been provided, it is generally believed that it is safest for preoperative patients to avoid use of supplements known to affect the coagulation system for 1-2 weeks before scheduled surgery.(10)

After passage of the Dietary Supplement Health and Education Act [DSHEA] in 1994, a new regulatory system was created for the safety and labeling of dietary supplements, as well as establishing a formal definition. Instead of receiving pre-market approval by the FDA as with prescription medications, the responsibility falls to the manufacturer to ensure that a dietary or herbal product is safe and that advertising claims are correct.(11) But product quality and safety have become continuing concerns for the supplement industry, (12) whether it involves herbal products or vitamin and mineral supplements.

Sometimes supplements are marketed for purposes other than their traditional uses. For instance, ephedra was traditionally used in China as a short-term treatment for a respiratory condition, but in the United States, ephedra is sold as a stimulant and used for extended periods for weight loss.

The potential for interaction with prescription medications is another concern. According to an advisory issued by the FDA in February of 2000, the popular herbal supplement St. John's Wort may reduce the effectiveness of common medications used for birth control, heart disease, and depression. St. John's Wort has also been found to interfere with traditional cancer treatments, and may endanger organ transplant success by decreasing cyclosporin levels.(13)

The side effects of supplements range from the known to the unknown. They can be relatively benign, such as valerian causing mild stomach upset (14) to previously unknown serious side effects with significant medical implications. For instance, saw palmetto is generally regarded as safe and nearly free of side effects, but one recent case report indicated that saw palmetto caused excessive bleeding during surgery. Although it was only a single incident, this may be important information for individuals planning to undergo surgery, or for those taking a medication that has a blood-thinning effect, such as aspirin or warfarin.(15)

Product impurities or batch-to-batch variability may also result in adverse effects and interactions with conventional medications. Another problem encountered is the potential for contamination, which can occur either in growing the plants or manufacturing the product. Microbiological, pesticide, and heavy metal contamination have led to recalls of some dietary supplements.(16) A study by the independent company, Consumerlab.com, revealed that 8 of 21 brands of ginseng contained unacceptable levels of pesticide residues, and two brands contained high levels of lead. A con-

sumer warning and recall was issued by the California State Health Director in February 2002 for "PC SPES" and "SPES" capsules after an investigation revealed that these products contained the undeclared prescription drug ingredients warfarin and Xanax (anti-anxiolytic), with the potential for serious health effects if not taken under medical supervision.(17) Inaccurate labeling has also been discovered. One firm had to recall its product because the actual folic acid content was only 35% of the amount claimed on the label. Another recall involved a product that was inadvertently ten times higher in niacin than what may be considered safe.(18) These examples illustrate the quality problems associated with a few of the more familiar supplements. Looking at the broader range of supplements, the FDA has received approximately 7,000 voluntary adverse event reports regarding dietary supplements since 1993, many of which they believe may be related to product mislabeling or adulteration.(16)

Recently, the Department of Health and Human Services issued a report following the evaluation of 100 labels for content and presentation with the following findings: 1) The safety information was usually incomplete or inconsistent regarding adverse reactions or side effects; potential interactions with other supplements, over-the-counter, or prescription drugs; maximum recommended dose; and contraindications, such as use during pregnancy. 2) Ingredient information was often incomplete and insufficient for consumers to understand what they were taking. The majority failed to identify the active ingredients or the ingredient amounts, and ingredient names were inconsistent across supplement labels, especially for botanicals, creating the potential for unaware consumers to take multiple doses of the same botanical, resulting in an overdose. 3) Information about benefits and risks was often unbalanced.(19)

There is some hope, however, for consumers such as hypothetical Jane Smith. In an attempt to address some of these quality problems, on March 7, 2003, the FDA proposed regulations to establish Current Good Manufacturing Practices [CGMPs] for manufacturers to follow. The proposed rules would help to ensure that dietary supplements and dietary ingredients are not adulterated with contaminants or impurities, and are labeled accurately to reflect the active ingredients and other ingredients in the product.(16) [see Table 4] It is anticipated that the implementation process for the new regulations may take three years for large firms, with smaller firms having until 2007 to comply. The proposed guidelines will also provide requirements for the design and construction of physical plants, quality control procedures, testing of the final product, handling consumer complaints, and maintaining records to demonstrate compliance with the regulations.(16)

Ms. Smith is not yet out of the woods, however. Although the proposal will require manufacturers to evaluate

the identity, purity, quality, strength, and composition of all dietary supplements, the new CGMPs do not address the efficacy of dietary supplements. They will not ensure that supplements perform as expected, and safety issues will continue to exist in regard to the active ingredient itself causing adverse reactions.(20)

Very few controlled trials involving supplements have been undertaken. However, this FDA action may also encourage more research on dietary supplements to improve the scientific evidence regarding their safety and effectiveness.(18) One limiting factor is the cost of research. Many herbal remedies cannot be patented, and manufacturers believe they would be unable to recoup the expenditures required for such studies. NCCAM was mandated to conduct research into complementary medicines and techniques, but only a few therapies could be evaluated on the limited budget of \$68.7 million for 2000.(21)

Manufacturers must ensure that claims made about dietary supplements are substantiated by evidence to show they are not false or misleading. Unlike prescription drugs, these products do not need approval by the FDA before being marketed. Manufacturers are not permitted to promote the product as a treatment, prevention, or cure for a specific disease or condition.(11) The FDA does allow manufacturers to use three types of claims on their labels. The first type represents health claims categorized as authorized health claims, health claims based on authoritative statements, and qualified health claims. The second type is a structure-function claim accompanied by a disclaimer that the FDA has not evaluated the claim. The third permissible type is a nutrient content claim, such as "good source of" or "high in" a particular nutrient which usually has an established daily value.(22)

The Federal Trade Commission (FTC) regulates the advertising of dietary supplements.(11) Recently, the FTC cited the marketers of a coral calcium supplement for making false and unsubstantiated claims about their product's health benefit by claiming that it can treat or cure cancer and other diseases. The FDA and FTC also sent strong warning letters to Web site operators marketing coral calcium to remove false or deceptive claims from their sites immediately.(23) The FTC also brought three enforcement actions against direct marketers of weight loss products containing ephedra in July 2003. The complaints and stipulated final judgments are available at <http://www.ftc.gov>.

What's New on the Horizon?

The National Institutes of Health's Office of Dietary Supplements has developed an evidence-based review program to assess the available scientific evidence on dietary supplements' efficacy and safety. These reviews will help the NIH establish research agendas for dietary supplements.(24) Resources for consumers and professionals are available on the NIH web site, including information on a supplement's indications for use, its known interactions with medications, and references to published scientific data.

Recent government actions could ultimately be a positive factor for the industry, by signaling to consumers that someone is looking out for their safety. (25) In the past few years, the perception that the natural health business is an unregulated industry has affected the dietary supplement business financially. Slowdowns in sales of some products have caused investors to take a wait-and-see attitude toward the industry. Rebecca Madley-Wright, editor of *Nutraceuticals World*, has reported there is \$300 million waiting on the sidelines to be invested in this area. Tighter regulation may well improve the prospects of the industry by driving out unethical practitioners. (2)

Manufacturers must ensure that claims made about dietary supplements are substantiated by evidence to show they are not false or misleading.

Conclusion

Consumer education is paramount. More information is becoming available to consumers and professionals to help them make informed decisions. There are numerous government web sites, professional association resources such as the American Dietetic Association, and various private or non-profit organizations that provide data regarding safety, quality, and research on dietary supplements. Identifying reputable sources continues to be a problem, as consumers often believe advertisements appearing in newspapers, television or the internet. Medical professionals need to be aware that their patients may be listening to other sources of information, and be prepared to offer sound medical advice in regard to dietary supplements and herbal products.

Upon discharge from the hospital, the hypothetical Jane Smith received instructions from a dietician to avoid sudden increases in foods that are high in vitamin K, such as broccoli, cabbage, green tea, spinach, and liver, as well as to avoid certain supplements and herbal teas containing coumarin. In addition, the dietitian provided some guidance through the tangle of information that surrounds any dietary supplements she may wish to take in the future. This review material was

also made available to the physicians who will continue to care for Ms. Smith, so that they may help reinforce the instructions. Ms. Smith will need to raise her level of awareness about the safety issues surrounding these herbal products, as they are subject to looser standards of labeling, purity, safety, dose, and efficacy than those required for medications.(26)

In spite of negative press and decreased consumer confidence, consumers continue to buy dietary supplements. This was evidenced by the recent boost in multivitamin sales after *JAMA* published an article indicating that all Americans should take a multivitamin daily. Furthermore, following the news that hormone replacement therapy may increase a woman's risk for heart disease and breast cancer, sales of natural estrogen alternatives, such as black cohosh and soy, grew by 32.5% and 7.6% respectively.(25) Consumers want these products, and it is expected that the dietary supplement industry will continue to grow despite occasional reports of side effects. This should be kept in mind when reviewing and interpreting medical records, as it may be another risk factor to investigate.

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Table 1a. Common Coagulation Laboratory Studies (30)

Prothrombin Time (PT). Normal 10-13 seconds. Evaluates the extrinsic coagulation system; aids in screening for some congenital factor deficiencies; assess warfarin effect; liver failure, vitamin K deficiency screen; disseminated intravascular coagulation (DIC).

Partial Thromboplastin Time (PTT). Normal 25-29 seconds. Evaluates intrinsic coagulation system; monitor heparin therapy; aids in screening for some congenital factor deficiencies; vitamin K deficiency, liver failure, DIC.

Activated Clotting Time (ACT). Normal varies between labs. Monitors heparin effect during cardiopulmonary bypass surgery; screen for coagulation deficiencies.

Coagulation Factor Assay. Tests for specific clotting factors. Avoid warfarin therapy for 2 weeks and heparin for 2 days prior to testing.

D-Dimer. Screening test for detection of deep vein thrombosis, acute myocardial infarction, and disseminated intravascular coagulation (DIC).

Fibrinogen. Coagulation protein and acute phase reactant. Interpretation difficult since multiple factors may affect level.

Platelet Count. Used in evaluation of bleeding disorders. Further evaluation may include platelet antibody, aggregation, and adhesion testing.

Table 1b. Common Liver Function Laboratory Studies (30)

Alanine Aminotransferase (ALT, SGPT). Liver test; more specific for liver injury than AST (SGOT).

Aspartate Aminotransferase (AST, SGOT). Primarily used to evaluate function; may be elevated in wide range of disease entities.

Bilirubin. Elevated in various liver and other diseases; large number of drugs may cause jaundice. Can be fractionated into direct and indirect components.

Gamma Glutamyl Transferase (GGT). Biliary enzyme useful in diagnosis of obstructive jaundice, intrahepatic cholestasis, and pancreatitis.

Hepatitis Profile. May include screening for hepatitis A, B, C, and/or D; antibodies and antigens may be evaluated; aids in detection of the stage of hepatitis.

Table 2. Common foods that interact with warfarin

Algae, purple laver, konbu, hijiki	Chive, raw	Oils (salad, soybean, canola)
Apple, green peel	Chrysanthemum, garland	Onion, green scallion, raw
Broccoli	Green leafy vegetables	Summer squash, peel only
Brussels sprouts	Green tea leaf, dry	

Table 3. Supplements affecting coagulation. (10, 27, 28, 29)

Agrimony	Capsicum	Ginseng	Poplar
Alfalfa	Cassia	Goldenseal	Prickly ash (northern)
Aloe gel	Celery	Horse chestnut	Quassia
Angelica (Dong Quai)	Chamomile	Horseradish	Red clover
Aniseed	(German and Roman)	Inositol nicotinate	Senega
Arnica	Clove	Kava	Sweet clover
Asa foetida	Dandelion	Licorice	Sweet woodruff
Aspen	Danshen	Meadowsweet	Tamarind
Black cohosh	Fenugreek	Mistletoe	Tonka beans
Black haw	Feverfew	Nettle	Wild carrot
Bladder wrack	Fish oil	Onion	Wild lettuce
Bogbean	Garlic	Parsley	Willow
Boldo	German sarsaparilla	Pau d'arco	Wintergreen
Bromelains	Ginger	Passion flower	Yarrow
Buchu	Ginkgo biloba	Policosanol	

Table 4.

Proposed CGMP rules would prevent:	<ul style="list-style-type: none"> • Drug contamination of product. • Other contamination (bacteria, pesticide, glass, lead). • Foreign material in product container. • Improper packaging. • Mislabeling
<ul style="list-style-type: none"> • Potentially harmful extra ingredients not listed on the label. • Missing or reduced active ingredients compared to the label. • Inclusion of incorrect ingredients in formulation. 	

OTHER RESOURCES ON HERBAL MEDICINES

Government Resources:

- A. US Food & Drug Administration Center for Food Safety & Applied Nutrition, <http://www.cfsan.fda.gov>
- B. MEDLINE Plus Health Information, www.nlm.nih.gov/medlineplus
- C. The International Bibliographic Information on Dietary Supplements (IBIDS) NIH-Office of Dietary Supplements, <http://ods.od.nih.gov>
- D. Food and Nutrition Information Center Dietary Supplements Resource List, <http://www.nal.usda.gov/fnic>
- E. The National Center for Complementary and Alternative Medicine (NCCAM) of the National Institutes of Health, <http://nccam.nih.gov/health>
- F. Office of Dietary Supplements (ODS) of the National Institutes of Health, (provides Fact Sheets on Dietary Supplements) <http://dietary-supplements.info.nih.gov>

Other Resources:

- A. Quackwatch, <http://www.quackwatch.org>
- B. SupplementWatch, Inc, <http://supplementwatch.com>
- C. The Dietary Supplement LLC, <http://www.TheDietarySupplement.com>
- D. Consumerlab, <http://www.consumerlab.com>
- E. US Pharmacopeia, <http://www.uspdsvp.org>

In Follow Up:

The last edition of the *MIM Reporter* discussed “The Global Epidemic of Overweight and Obesity”. Of interest, the FDA has scheduled a public meeting on obesity for Oct. 23, 2003. This meeting is sponsored by the FDA Obesity Working Group.

As reported on the FDA web site (www.fda.gov), the meeting will focus on six questions related to obesity:

1. What is the available evidence on the effectiveness of various education campaigns to reduce obesity?
2. What are the top priorities for nutrition research to reduce obesity in children?
3. What is the available evidence that FDA can look to in order to guide rational, effective public efforts to prevent and treat obesity by behavioral or medical interventions, or combinations of both?
4. Are there changes needed to food labeling that could result in the development of healthier, lower calorie foods by industry and the selection of healthier, lower calorie foods by consumers?
5. What opportunities exist for the development of healthier foods/diets and what research might best support the development of healthier foods?
6. Based on the scientific evidence available today, what are the most important things that FDA could do that would make a significant difference in efforts to address the problem of overweight and obesity?