CONNING

Conning the IADC Newsletters

Recognizing that a wide range of practical and helpful material appears in the newsletters prepared by committees of the International Association of Defense Counsel, this department highlights interesting topics covered in recent newsletters and presents excerpts from them.

Dietary Supplements and the Playing Field

Writing in the April newsletter of the Drug, Device and Biotech Committee, Steven M. Kohn and Courtney E. Quinn of the Oakland, California, office of Crosby, Heafey, Roach & May discuss the alleged dangers emanating from dietary supplements:

Athletes and fitness buffs alike take ephedrine supplements to enhance performance, bulk up or slim down. Yet in the past few years, the alleged dangers posed by dietary supplements containing ephedrine have engendered world-wide media scrutiny. Numerous stories about adverse health impacts related to the supplements may force the U.S. Food and Drug Administration to finalize regulations currently under consideration or to use existing mechanisms to further monitor dietary supplements.

Armed with knowledge of current federal regulations and the FDA's proposed regulations regarding ephedrine alkaloid-containing supplements, members of the dietary supplement industry can be proactive to prevent potential lawsuits and/or government enforcement actions.

Background on ephedrine

Ephedrine and related alkaloids are the primary ingredients in many dietary supplements sold in drug stores, pharmacies and supermarkets. These products are marketed for a variety of purposes: weight loss, body building, increased energy and as an aid to asthma sufferers. Ephedra, the botanical source of ephedrine alkaloids, has been used in Chinese medicine for more than 5,000 years. Ephedra is sometimes referred to as Ma Huang, Bishop's Tea or Chi Powder. *See* "Products That Consumers Inquire About," www.cfsan.fda.gov/dms/ds-prod.html.

Ephedra and ephedrine alkaloid-containing products, according to the FDA, stimulate the nervous system or heart in a manner similar to amphetamines. Of the 800 reports of adverse events received by the FDA involving more than a hundred dietary supplement products, the most common and consistent finding is the presence of ephedrine alkaloids. To date, the FDA has investigated and reported 140 adverse event reports associated with ephedrine alkaloids, ranging from high blood pressure, heart rate irregularities, insomnia, nervousness, tremors and headaches, to seizures, heart attacks, strokes and death. 62 Fed.Reg. 30677-79, 30690 (June 4, 1997).

Nevertheless, even critics of ephedrine alkaloid-containing products concede that these adverse event reports do not provide scientific proof that ephedrine-containing dietary supplements cause these reactions. *See* Ephedra Education Council, "The Facts About Ephedra," www.ephedrafacts.com/thefacts.html.

According to the *Nutrition Business Journal* (November/December 2001), the dietary supplement industry made $16.8 billion dollars in sales profits in 2000. In the same year, sales of herbal supplements exceeded $4.1 billion. Dietary supplements containing ephedrine alkaloids alone constitute a billion dollar industry. The ephedrine alkaloid-containing supplements reach a wide audience—from high school athletes looking to gain a competitive edge, to women looking to lose unwanted pounds. The volume of sales, the wide audience and the recent press coverage regarding ephedrine may leave members of the dietary supplement industry vulnerable to potential lawsuits and possible regulatory enforcement.

Supplements and sports

In 1999, dietary supplements first made headlines in the arena of alleged sports-related injuries when Anne Marie Capati, a New York woman, died after suffering a stroke at Crunch Fitness in Manhattan. Capati's husband sued the fitness club, alleging his wife's trainer encouraged her to buy supplements containing ephedrine. For months following Capati's death, articles and press coverage questioned the safety of the dietary supplements. *See* Marilyn Chase, "Workout Fatality Puts Focus on Gyms and Supplements," *Wall Street Journal*, June 28, 1999, at B1; Terry Pristin, "Health Club and Trainer Are Sued in Death, *New York Times Abstracts*, June 29, 1999.

While the debate over the safety of ephedrine alkaloid-containing supplements continues, media coverage of dietary supplements has resurfaced in the past year. The new wave of discussion began on September 27, 2001, when the National Football League became the first professional sports organization to ban products containing ephedrine alkaloids. Although the National Collegiate Athletic Association and the International Olympic Committee already had banned these products, no professional organization had done so.

Under the NFL ban, players are prohibited from taking, distributing or having ephedrine alkaloids on club premises. The ban additionally prohibits players from endorsing companies that make or sell the prohibited substances, and an NFL player cannot endorse a non-ephedrine product if the manufacturer also produces a product that contains ephedrine alkaloids.

Following the NFL ban, an association of responsible manufacturers and distributors, the Ephedra Education Council (EEC), reiterated that scientific and medical evidence has found that ephedra-containing supplements are safe and effective when used properly. *See* Ephedra Education Council, "Use of Ephedra Dietary Supplements by Athletes," www.ephedrafacts.com/oct2.htm

Many NFL players believe the league's ban is a knee-jerk reaction to recent football-related deaths. In 2001, 16 football players died nationwide, ranging from the middle school level to professional. The death of Minnesota Vikings' lineman Korey Stringer especially intensified concerns about ephedrine-related supplements. While many believe Stringer's death to be heat related, rumors of his ephedrine use have surrounded his death. *See* Stefan Fatsis, "On Sports: Muscling Out Supplemental Income," *Wall Street Journal*, November 30, 2001.

While the NCAA banned ephedrine use in 1997, a *USA Today* survey shows that collegians still are using ephedrine-related products. College level football players' deaths brought additional attention. In August 2001, Rashidi Wheeler, a Northwestern University player died after collapsing during a team running drill. A medical examiner found ephedrine in his blood. In February 2001, Devaughn Darling, a Florida State football player, died after a football workout. Darling's autopsy report revealed ephedrine in his system, possibly from cold medicine. *See* Gary Mihoces, "Ephedrine: Safe or lethal? Debate intensifies as supplement becomes the energy booster of choice for athletes," *USA Today*, November 8, 2001, at CO1.

Given this recent media attention, an analysis of federal regulations relating to these products is necessary for manufactur-

ers to remain vigilant and proactive in the industry.

Federal regulation

While lawmakers and plaintiffs' lawyers complain that the FDA is powerless against the manufacturers of these products, the FDA does have a wide variety of enforcement mechanisms already in place. These are (1) the Federal Food, Drug and Cosmetic Act (FD&C Act); (2) the Dietary Supplement and Health Education Act of 1984 (DSHEA); (3) the FDA's proposed rule; and (4) the FDA's and FTC's joint regulation of advertising and marketing.

FD&C Act

Before 1994 and DSHEA, the FD&C Act regulated dietary supplements in the same way as food additives. It required a dietary supplement manufacturer to obtain pre-market approval for food additives or demonstrate that such ingredients were "generally recognized as safe" before marketing the product. 21 U.S.C. § 321. If the product was not generally recognized as safe, or if the FDA challenged the determination that the product was generally recognized as safe, then the manufacturer was required to file a food additive petition establishing the product's safety. 21 U.S.C. § 348.

Because of the costly petition process under the FD&C Act, dietary supplement manufacturers and distributors pressed Congress to deregulate. This effort was successful, resulting in DSHEA. *See* Ilene Ringel Heller, "Functional Foods: Regulatory and Marketing Developments," 56 *Food Drug Cosmetic Law Journal* 197, 198 (2001).

DSHEA

The sentiment that the dietary supplement industry is unregulated began in 1994 when Congress passed the DSHEA. It created an entirely new regulatory scheme for dietary supplements. Under it, dietary supplements are categorized within "foods," not drugs. Therefore, many members of the public perceive no regulation at all. *See* Jim Lassiter, "Cooperative Enforcement: A New Approach to Dietary Supplement Regulation and Enforcement," *Update*, eds. FDLI, Issue 6 (November/December 2001).

Definitions. A product must meet the definition of a dietary supplement to full under the DSHEA. A "dietary supplement" is a product taken by mouth that contains a "dietary ingredient" intended to supplement the diet. 21 U.S.C. § 321(ff). If the product meets this definition, it will be regulated as food.

In order for an ingredient of a dietary supplement to be a "dietary ingredient," it must be one or any combination of these substances: (1) a vitamin, (2) mineral, (3) an herb or other botanical, (4) an amino acid, (5) a dietary substance used to supplement the diet by increasing the total dietary intake, or (6) a concentrate, metabolite, constituent or extract.

A dietary supplement must be intended for ingestion in pill, capsule, tablet or liquid form. Additionally, a dietary supplement may not be represented for use as a conventional food or as a sole item of a meal or diet. 21 U.S.C. §§ 321(ff)(2)(A)(i), 411(c)(1)(B)(ii), and 321(ff)(2)(B).

A "new dietary ingredient" is an ingredient that meets the definition for a "dietary ingredient" but was not sold in the United States in a dietary supplement before October 15, 1994. *See* "Overview of Dietary Supplements," www.cfsan.fda. gov/~dms/dsoview.html. *See also* 21 U.S.C. § 350(b).

Requirements. Manufacturers of dietary supplements containing both dietary ingredients marketed before 1994 and "new dietary ingredients" must meet some requirements before marketing these products. First, the manufacturer or distributor must determine that the dietary supplement is safe. However, manufacturers of dietary supplements with ingredients marketed before 1994 do not need to provide the FDA with evidence of the ingredients' safety. Second, the manufacturer or distributor must determine that any claim or representation is substantiated by adequate evidence to show that these claims are not

false or misleading. 21 U.S.C. § 343-2(a)(1).

If the "dietary ingredient" was marketed prior to October 15, 1994, the manufacturer may market it without notice or substantiation of safety.

If the dietary supplement contains a "new dietary ingredient," it can be marketed only after 75 days notice to the FDA and substantiation that the dietary ingredient is "reasonably expected to be safe." 21 U.S.C. § 350(a). Therefore, a dietary supplement containing a new dietary ingredient is subject to more requirements prior to marketing than is a dietary supplement with an ingredient marketed before October 15, 1994.

Furthermore, unlike manufacturers of drugs or medical devices, manufacturers of dietary supplements are not required to report adverse events to the FDA.

Safety. Under the DSHEA, once the product is on the market, the FDA bears the burden of proving the product is unsafe (*i.e.*, "adulterated") before it can take regulatory action by restricting the product's use or by removing the product from the market. The FDA works under 21 U.S.C. § 342, which governs "adulterated foods." A dietary supplement is "adulterated" if it or one of its ingredients presents "a significant or unreasonable risk of illness or injury" when used as directed on the label or under normal conditions of use, if there are no directions. 21 U.S.C. § 342(f)(1)(A). A product also may be "adulterated" if a dietary supplement or dietary ingredient poses an imminent hazard to public health or safety. 21 U.S.C. § 342(f)(1)(C).

A dietary supplement that contains a "new dietary ingredient" is "adulterated" when there is inadequate information to provide reasonable assurance that the ingredient will not present a significant or unreasonable risk of illness or injury. 21 U.S.C. § 342(f)(1)(B).

The FDA often cannot establish that a product presents a significant or unreasonable risk of illness or injury, or poses an imminent hazard to public health or safety. To remove a product from the market, the FDA must build a strong case that the product causes harm to the public. This process takes years and requires the FDA to develop strong scientific evidence. Because the FDA's burden is so high, it has taken to issuing public warnings, rather than declaring that a dietary supplement is adulterated. *See* Heller, *supra*, at 199. For instance, the FDA, together with the Department of Health and Human Services, has issued warnings related to ephedrine alkaloid-containing dietary supplements.

The FDA issued a "Medical Bulletin" in September 1994, "Adverse Events with Ephedra and Other Botanical Dietary Supplements," alerting consumers that it had received a high number of adverse event reports associated with ephedrine-containing products marketed as dietary supplements for weight loss, energy, performance-enhancing and body-building purposes. Available at www.cfsan.fda.gov/~dms/ds-ephe2.html.

In 1997, it issued a "Talk Paper," noted above, warning users of dietary supplements being promoted as an "herbal alternative" to "fen-phen." The paper noted that these products were considered a drug and that the agency was taking regulatory action.

Nutritional support statements

Under the DSHEA, a dietary supplement cannot be promoted as a prevention, mitigation, treatment or cure for a specific disease. 21 U.S.C. § 343(6)(A)-(C). A dietary supplement that claims to treat or cure an ailment also must be approved as a new drug under the provisions of the FD&C Act. If a dietary supplement does make such claims, it is an illegal drug.

Under the DSHEA, a manufacturer may make a "health claim"—such as the claim that calcium may reduce osteoporosis—if the claim is not false or misleading. 21 U.S.C. § 21 U.S.C. 343(6)(B). These "health claims" must be authorized by an FDA finding that there is "significant scientific agreement" to support the claim or that the claim is based on "authoritative statements" from a well- established scientific body. *See* www. ftc.gov/bcp/conline/

pubs/buspubs/dietsupp.htm.

Additionally, the manufacturer can make a labeling claim regarding the effects of consuming the product on the "structure or function" of the body. These claims do not require prior FDA approval, but they do require 30 days notice to the FDA. If the product makes such a claim, the label must bear the 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." 21 U.S.C. §§ 343(6)(B) and 343(6)(C). *See* http://vm.cfsan.fda. gov/~dms/dietsupp.html. Both types of claims must be truthful and not misleading.

Labeling requirements

Dietary supplements, like all other foods, have labeling requirements. If the manufacturer does not comply with the requirements, the supplement will be deemed "misbranded" under the DSHEA.

Dietary supplement labels must include the name and quantity of each "dietary ingredient" or, for proprietary blends, the total quantity of all dietary ingredients. 21 U.S.C. § 343. The label also must identify the product as a "dietary supplement" (*e.g.*, vitamin C dietary supplement). The label must provide nutrition labeling, listing dietary ingredients present for which the FDA has established daily consumption recommendations. If a dietary ingredient is not in "significant amounts," then it does not need to appear on the label.

Good manufacturing practices

The DSHEA grants the FDA authority to develop good manufacturing practice regulations for dietary supplements. The FDA may create regulations that are modeled after "current good manufacturing practice regulations for food." It may not prescribe regulations for which there is no current and generally available analytical method. 21 U.S.C. § 342(g). However, the agency has not yet prescribed any regulations.

FDA's proposed rule

In addition to current federal regulations governing all dietary supplements, the FDA has proposed regulations that would specifically govern ephedrine alkaloid-containing dietary supplements. At this stage, the regulations are still pending, but if these regulations pass, they would subject manufacturers and distributors of dietary supplements to two additional requirements.

Between 1993 and 1997, the FDA received more than 800 reports of illnesses and injuries (called adverse event reports, or AERs) associated with more than a hundred different dietary supplements products that contained ephedrine alkaloids. The events included high blood pressure, heart rate irregularities, insomnia, nervousness, tremors, headaches, seizures, heart attacks and strokes. It reviewed adverse events of all products showing cardiovascular system and nervous system complications and found that approximately 50 to 60 percent of these were associated with dietary products containing ephedrine. 62 Fed.Reg. at 30679.

To address the concerns associated with ephedrine alkaloid-containing products, on June 4, 1997, the FDA published a proposed rule regarding dietary supplements containing ephedrine. It contained six provisions. In 2000, the FDA withdrew four of the six proposed regulations. 65 Fed.Reg. 17474. The following discussion covers all the 1997 proposals, the provisions that were withdrawn, and the provisions that remain.

Four withdrawn proposals

The FDA initially offered four proposed regulations in the following areas:

- a per serving limit of 8 mg,
- a total daily intake limit of 24 mg,
- a ban on using ephedrine alkaloid-containing products for more than seven consecutive days, and
- a limit on claims that would promote (1) long-term use, (2) short-term excessive use, or (3) use of the product as an alternative to street drugs.

The House Committee on Science requested that the Government Accounting Office (GAO) examine the FDA's scientific bases for the proposed rule and

whether the agency adhered to federal rulemaking requirements. The GAO found the FDA's scientific basis lacking. It concluded that the FDA was justified in concluding that the number of adverse events associated with these supplements warranted the FDA's attention, but it recommended the FDA provide stronger evidence linking ephedrine alkaloid containing supplements to the proposed dosage, daily intake and duration of use limits. 65 Fed.Reg. at 17475.

Following the GAO report, the FDA withdrew the dosage, daily limit, duration of use and claims provisions. It is reassessing the proposed approaches in the above four areas.

Surviving proposed regulations

Prohibition of ingredients with stimulant effects. One of the two remaining proposed regulations would prohibit dietary supplements that mix ephedrine alkaloids with other ingredients with known stimulant effects (*e.g.*, caffeine, yohimlane). 62 Fed.Reg. 30695-30696. In 1997, the FDA tentatively concluded that any dietary supplement that contains ephedrine alkaloids in combination with an ingredient that produce stimulant effects presents a "significant or unreasonable risk of injury or illness under the conditions of use suggested in the labeling or under ordinary circumstances of use and are adulterated," and is thereby adulterated.

The FDA proposed this provision in response to a number of adverse events involving supplements combining ephedrine alkaloids and stimulant ingredients.

Warning label statements. The other proposed regulation would require warning statements in certain situations containing the following elements: (1) cautions that consumers not use the product if they have certain diseases, health conditions or are using specific drugs; and (2) cautions alerting the customer to stop using the product if certain signs or symptoms develop.

The FDA proposed this regulation because it tentatively concluded that persons with certain diseases, or persons taking certain medications known to adversely react with ephedrine alkaloids, are at risk of suffering adverse events. The agency believes in the above situations that ephedrine use at any level will cause adverse reactions.

Advertising and marketing.

Another significant area of federal regulation and enforcement has been dietary supplement advertising and marketing. The Federal Trade Commission and the FDA have a long-standing liaison agreement to share responsibility with regard to dietary supplements. Under this agreement, the FDA has primary authority for regulating claims made on the product's labels or packaging, while the FTC has primary authority for regulating claims made in advertising and commercial broadcasts. *See* "Dietary Supplements: An Advertising Guide for Industry," available at www.ftc.gov/bcp/conline/pubs/buspubs/dietsupp.htm.

Because of the shared jurisdiction, the two agencies work closely to ensure their efforts are consistent. For instance, under the DSHEA, supplement makers can make two types of claims on product labels: (1) "health claims," such as a claim that calcium may reduce osteoporosis, and (2) "structure/function" claims, those that relate to the effect of the nutrient on the body.

The FDA approves "health claims" by determining whether there is adequate support. "Structure/function" claims do not need FDA approval, but they do require 30 days notice to the FDA. Under the DSHEA, both types of claims must be truthful and not misleading. When it analyzes whether claims made in advertising violate its "truth in advertising" law, the FTC gives great deference to the FDA's determinations of adequate support and of whether the claims are truthful and not misleading.

The most recent joint enforcement effort has focused on dietary supplement marketing and advertising on the Internet. Since 1997, the FTC and FDA, along with other

enforcement authorities, have been combating fraudulent advertisements and marketing in cyberspace in a program called "Operation Cure.All." In 2001, under its newly appointed chairman, Tim Muris, the FTC took enforcement actions against eight Internet marketers of dietary supplements for fraudulent promotions. *See* Michelle Rusk, "Operation Cure.All: FTC Joins Forces with FDA and Other Government Agencies to Combat Health Fraud on the Internet," *Update*, eds. FDLI, Issue 6, page 4 (November/December 2001).

In June 2001, Chairman Muris announced that the agency was going to step up its efforts to combat fraud on the Internet. Large-scale Internet monitoring efforts are under way, and the FTC plans on targeting more companies.

Deep Venous Thrombosis and Airline Travel

Writing in the April newsletter of the Aviation and Space Law Committee, Tory Weigand of the Morrison, Mahoney & Miller, Boston, says the jury is still out on this one:

Medical aid related claims asserted by airline passengers against airlines continue to arise and present unique issues for defense counsel. The avant-garde of these claims are coined as "economy class syndrome" or "travelers thrombosis." These claims are being brought as "test" cases in various venues, including courts in the United States, the United Kingdom and Australia.

Thrombosis: A primer

Economy class syndrome or travelers thrombosis is the popular name given to airline passengers who are reported to have suffered a deep vein thrombosis (DVT) or venous thromboembolism (VTE). A thrombosis is the medical term for the formation of a blood clot in a blood vessel. A clot is the collection or clump of various blood cells. If the clot forms and remains attached at the point of its formation and partially or completely blocking the free flow of blood through the vessel, it is a thrombus. The thrombus becomes an embolism if it breaks free and travels to a different part of the circulatory system. Emboli, in turn, are pieces of the clot that break off as the clot grows—that is, "propagation."

Thrombosis can occur in both the veins and arteries. When thrombosis occurs in an artery, the body tissues usually supplied with blood suffer an infarction or death as a result of a lack of blood-borne nutrients.

There are various types of thrombosis, depending primarily on where they occur. A coronary thrombosis, for instance, is a clot and blockage of an artery to the heart, which can (and usually does) result in a heart attack (myocardial infarction). A cerebral thrombosis is a clot or thrombosis in an artery leading to the brain, which usually results in a stroke.

Vein thrombosis also takes different forms. Where a clot forms in a vein located near the surface of the skin, it leads to a condition known as thrombophlebitis, which results in swelling and inflammation where the clot develops in the vein. A deep vein thrombosis is a clot that arises in a vein deep in the body. A common area where they can arise is the calf or thigh as blood can move relatively slowly in these areas. Other veins where the clot can form are veins in the pelvis, abdomen and even the heart. A clot in a vein that becomes lodged in a vessel of the lung is called a pulmonary embolism.

The pressure at which the heart pumps blood through arteries throughout the body's organs is dissipated by the capillaries making the blood's return through the veins less vigorous. However, veins do not have thick muscular-like walls and are not able to help pump blood to different parts of the body as arteries do. Instead, blood moves through the veins by either gravity or by the contraction of surrounding muscles, which squeezes blood in the veins back to the heart using a system of one-way valves. The main leg veins are located deep within the leg muscles and the one-way valves enable muscle action to augment the pumping action of the heart.

This has perceived significance in