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Dietary Supplements: Ephedra

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Summary

Ephedrine is a natural constituent of the herb ephedra and a synthetic compound present in certain over-the-counter drug products. The herbal form, known as Ma Huang in China, has been used as a remedy for asthma. In western cultures, ephedrine, the active drug product ingredient, has been used as a bronchodilator and decongestant for various respiratory problems. More recently, dietary supplements containing ephedra have been promoted for weight reduction and as a performance enhancer in body building and other sports.

Under the provisions of the Dietary Supplement Health and Education Act of 1994 (DSHEA), the Food and Drug Administration (FDA) must show that a supplement is unsafe and causes harm before it can be removed from the market. In 1997, following several hundred reports of adverse effects alleged to be caused by ephedra use, FDA proposed rules to restrict the dosage, require specific warnings on ephedra-containing supplements, prohibit supplements containing ephedrine combined with other known stimulants, and require warnings against excessive intakes. This proposal was criticized for the lack of scientific evidence to support FDA's dosage limitations and the labeling requirements. In 2000, FDA withdrew part of the proposed rule, but subsequent high profile deaths attributed to ephedra led FDA to re-propose the original regulation in 2003. On December 30, 2003, the Department of Health and Human Services (HHS) and FDA announced plans to prohibit sale of ephedra, using the safety provisions of DSHEA for the first time.

Several congressional hearings have focused on the limitations of FDA's current adverse events reporting system, which was used by the agency to conclude that dosage restrictions and mandatory labeling were needed, and specific cases of death attributable to ephedra. A General Accounting Office report examined the scientific basis for FDA's ephedra proposal and concluded that the number of adverse events reports related to ephedra warranted agency attention to safety concerns but failed to provide adequate evidence to support the dosing levels and duration of use limits. In June 2002, HHS announced it would plan expanded research on ephedra's safety, following completion of a RAND Corporation report it had commissioned for review of the existing science. The RAND report indicated that the literature showed that although ephedra can promote a modest short-term weight loss in clinical trials, there is insufficient data on long-term benefits for weight-loss and body building. Combined with other stimulants, it was associated with increased health risks.

In the 108th Congress, H.Con.Res. 52 expresses the sense of the Congress that all major sports organizations should ban the use of ephedra. H.R. 725 would establish labeling and advertising rules for supplements containing ephedra and prohibit sales to minors. H.R. 1025, the Ephedra Public Protection Act, would require pre-market approval for supplements containing ephedra alkaloids and post-market reporting of serious adverse effects. S.Res. 260 expresses the sense of the Senate that the Secretary of HHS should take action to remove ephedra from the market. These bills were referred to the appropriate committees, but no additional action has yet been taken on any bill or resolution.

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Dietary Supplements: Ephedra

Background

Ephedrine is the pharmaceutically active compound found in both natural form in herbal ephedra and the synthetic ingredient present in certain over-the-counter (OTC) drug products.¹ Recent attention to the dietary supplements containing ephedra and their regulatory status has been of concern to Congress, the supplement industry and consumers. This report will attempt to clarify the current regulatory status of dietary supplement products containing ephedra.

Ephedra is a botanical, whose herbal properties have been known for centuries by the name of Ma Huang in China, where it was first used as a remedy for the treatment of bronchial asthma. Although some 40 species are known worldwide, its herbal and pharmaceutical effects are attributable to the contents of ephedrine and related alkaloids found primarily in the species of Chinese origin. Historically, practitioners of traditional medicine in China have been trained in the art and skills of compounding small amounts of a variety of botanical ingredients, including ephedra, to treat specific conditions. Ma Huang has generally been consumed in the form of an invigorating tea or infusion with beneficial effects on respiration. Most recently, ephedra in pill form has been promoted for weight reduction and as a performance enhancer in body building and other sports.

In western cultures, ephedrine has been used for years in various drug products. Ephedrine is mainly used as an ingredient in bronchodilator and decongestants, for treating asthma and hayfever, and to combat circulatory collapse in reaction to anesthesia, poisoning, shock and allergic reactions.

The pharmaceutical effects of ephedra are due to the ephedrine alkaloids, but the herbal product may not have the same physiological effect as the pure compound, which can be produced synthetically. The ephedra herb has been used for similar medical purposes, although dietary supplement advocates claim that its action is more gentle and less likely to cause adverse effects. However, a report that investigated the pharmacokinetics of ephedrine from three commercially available herbal Ma Huang products, compared to 25 milligrams (mg) ephedrine hydrochloride capsules showed that the products had similar effect.² The authors reported that

¹ Note: Since ephedrine is the active chemical present in both dietary supplements and OTC drug products, the term ephedra will be used to refer to the dietary supplement (natural) form and ephedrine will refer to the drug (synthetic) form for purposes of this report.

² Gurley, B., et al. Ephedrine pharmacokinetics after ingestion of nutritional supplements containing *Ephedra sinica* (Ma Huang). *Therapeutic Drug Monitoring*. 1998. v. 20, pp. 439-445.

recent increases in Ma Huang toxicity were not due to the differences in the absorption rates of botanical ephedrine compared with synthetic ephedrine, but instead resulted from accidental overdose often promoted by off-label claims and a belief that natural medicinal agents are inherently safe.

The Dietary Supplement Health and Education Act of 1994 (DSHEA) exempted dietary supplements from the type of premarket approval process that drugs, medical devices and food additives must undergo before they are allowed to be sold. For medical devices and food additives, manufacturers must demonstrate to Food and Drug Administration (FDA) satisfaction that the products are safe through adequate scientific testing prior to marketing. In the case of prescription and OTC drugs, manufacturers must prove, through adequate and well-controlled investigations, that their products are safe and effective before they can be approved for marketing. However, Congress effectively shifted the burden of proof under DSHEA from the manufacturer to the agency to show that a dietary supplement is unsafe, a significantly more difficult standard to meet. Moreover, the agency must demonstrate that the dietary supplement causes harm before it can be removed from the marketplace. In the case of herbal supplements, FDA has only voluntary reports from consumers to rely on, along with generally limited scientific evidence. Very often ephedra is one of several supplements consumers are using, thus complicating a determination of the actual cause of an adverse reaction. Because the law does not require that these products undergo premarket testing and evaluation, there is no reliable baseline information on the possible side effects that can be used to anticipate or compare adverse events. Another confounding factor is research evidence that supplement users are less likely than other consumers to report adverse effects from a product they use.³

In contrast, when ephedrine is used in prescription or OTC products, it is regulated as a drug by FDA's Center for Drug Evaluation and Research (CDER). Ephedrine is used for treating mild forms of asthma, and is also approved by the agency for treating such conditions as hypotension, nasal congestion, and sinusitis. FDA considers nonprescription ephedrine to be safe and effective as a bronchodilator, preferably when used under a doctor's care. The dosage recommendations in adults and children over 12 years are 12.5 -25 mg every 4 hours, not to exceed 150 mg per day.⁴ According to the industry handbook, the principal adverse effects can include central nervous system (CNS) stimulation, sleeplessness, nausea, loss of appetite, tremors, tachycardia, and urinary retention.⁵ The handbook further indicates there are reports that chronic overdose of ephedrine may, in some patients, result in either severe cardiac toxicity or psychosis. Ephedrine, along with other CNS stimulants such as caffeine and phenylpropanolamine, are frequently used

³ Barnes, J., et al. Different standards for reporting ADRs to herbal remedies and conventional OTC medicines: face-to-face interviews with 515 users of herbal remedies. *Journal of Clinical Pharmacology*. v. 45, 1998. p. 496-500.

⁴ U.S. Department Health and Human Services (HHS). Food and Drug Administration. Cold, cough, allergy bronchodilator, and antiasthmatic drug products for over-the-counter human use. *Federal Register*. v. 56. Apr. 1, 1991. p. 190-197.

⁵ American Pharmaceutical Association. Handbook of Nonprescription Drugs. 12th Edition. 1999. Chapter 10. Asthma by D. M. Williams and T. H. Self. p. 229-230.

as ingredients in products manufactured to physically resemble much stronger controlled substances, such as amphetamines. To prevent both misuse and abuse with the OTC version of ephedrine, an FDA drug advisory committee recommended, and the agency subsequently proposed in 1995 an amendment for more stringent regulation of ephedrine, which is primarily contained in bronchodilators.⁶ However, the agency has not finalized the proposed rule on ephedrine in bronchodilators. Denmark, which has considerable research and use experience with ephedrine for weight loss, regulates it as a prescription drug. Recently, the World Health Organization proposed a restriction on the manufacture and distribution of ephedrine-containing bronchodilator products.

FDA's Proposal to Regulate Herbal Ephedra

In the 1990s, FDA began receiving reports that consumers were experiencing a variety of adverse effects, allegedly caused by ephedra use. After the agency accumulated several hundred reports of adverse effects, including a number of deaths, attributed to the supplement's use, it convened an ephedra working group, which included members of the FDA Food Advisory Committee and outside experts, on October 11-12, 1995. Following the testimony presented at its first meeting, the group reached no conclusions or determination whether FDA should take any action on regulating these supplements. At a second meeting on August 27-28, 1996, when additional information was reviewed, some group members indicated their concern that there was no safe level of this substance. Others, however, believed that there were certain levels that were safe for use of ephedra.

Subsequently, FDA proposed a rule for ephedra that addressed issues concerning its dosing, labeling and warning statements.⁷ The agency proposed that in supplement form a single dose should not exceed 8 milligrams and products should bear required labeling to indicate that no more than 24 mg should be taken in a given day. Also, labeling information was to indicate that the product should not be used for longer than 7 days and required a warning statement that the product was not for long-term use, such as for body building and/or weight loss. The agency also proposed to prohibit the use of ephedra in dietary supplements in combination with ingredients that have a known stimulant effect, such as caffeine, which might cause an interaction. In addition, FDA proposed that a statement accompany any claims that encourage short-term excessive intake to enhance a purported effect, such as increased energy, stating that consuming more than the recommended serving (dose) may result in serious adverse health effects, such as heart attack, stroke, seizure, or death. FDA proposed that these specific warning statements be required to appear on supplement labels when the product contained ephedra.

⁶ U.S. Department Health and Human Services (HHS). Food and Drug Administration. *Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-counter Human Use*. Proposed Amendment of Monograph for OTC Bronchodilator Drug Products. Notice of proposed rulemaking. *Federal Register* v. 60, no.144. July 27, 1995. p. 38643- 38647.

⁷ U.S. Department Health and Human Services (HHS). Food and Drug Administration. *Dietary Supplements Containing Ephedrine Alkaloids*. Proposed rule. *Federal Register* v. 62. June 4, 1997. p. 30678-30724.

FDA's proposed regulation generated considerable comment, primarily from consumers and the dietary supplement industry. Most critical comments claimed that FDA's ephedra dosage limitations were not based on scientific evidence, and its labeling requirements were excessive. The voluntary adverse events reporting (AERs) system, which had been the source of the agency's justification for proposing the regulatory changes, also came under scrutiny. The AERs data were criticized for being insufficient to determine whether the adverse events reported were actually caused by ephedra use.

As a result of the continued criticism of the agency's use of the AERs as the basis for its rulemaking, FDA announced in April 2000 that it was withdrawing certain provisions of the proposed rule on ephedra.⁸ The provisions that were withdrawn include the dietary ingredient limit for ephedra on a per serving basis, proposed compliance procedures for use of the high performance liquid chromatography method (for sample analysis), limitations on the duration of the product's use, and the prohibition on claims for long-term use, such as for bodybuilding and weight loss. The agency retained the sections of the proposed rule that would prohibit use of ingredients with stimulant effects in combination with supplements containing ephedra, and the requirement that products containing ephedra carry a warning statement on its use by consumers with certain diseases or health conditions or who use certain drugs, accompanied by a recommendation that use be discontinued if they experience certain signs or symptoms.

On March 31, 2000, FDA released 140 additional recent cases of adverse events associated with ephedra use.⁹ The agency indicated that these cases had been more fully reviewed and evaluated to determine whether ephedra was the likely cause of the adverse events. FDA also announced its intention to participate in a public forum to address these new adverse events reporting data. At that time, about 1200 cases of adverse events allegedly attributed to ephedra had been reported to the agency.

The Department of Health and Human Service's Office of Women's Health convened the Safety of Dietary Supplements Containing Ephedrine Alkaloids Public Meeting on August 8-9, 2000, to provide an opportunity to review the analysis of adverse events reports by FDA and outside experts. Additional public testimony on recent scientific information on ephedra use was also taken. The *Federal Register* announcement of the meeting sought comments on several questions concerning physiologic actions of ephedra, indications for its use, dosage and duration of use, and risks based on user demographics. It also sought comments on combination use with stimulants, exercise stress and individual sensitivities, and the outcomes associated with dose, user characteristics, and duration of exposure. The meeting revealed the considerable difference of opinion between government and outside reviewers on the evidence concerning the risks associated with using ephedra, based

⁸ U.S. Department of Health and Human Services (HHS). Food and Drug Administration. *Dietary Supplements Containing Ephedrine Alkaloids; Withdrawal in Part*. Proposed Rule. April 3, 2000. *Federal Register* v. 65, no. 64. p. 17474-17477.

⁹ U.S. Department of Health and Human Services (HHS). Food and Drug Administration. *Dietary Supplements Containing Ephedrine Alkaloids; Availability*. Notice. *Federal Register* v. 65, no.64. April 3, 2000. p. 17510-17512.

on AERs. Numerous private citizens provided both positive and negative testimonials regarding their personal experience with ephedra use: some reported life-changing weight loss, improvements in other health conditions, and increased energy, while others told of experiencing severe side effects after consuming even minimal doses. Several scientific investigators currently engaged in research on the use of ephedra for weight loss spoke at the meeting, but were unable to disclose the final results of their studies because they had not yet been peer-reviewed and accepted for publication. The summary of the meeting identified several needs: a reliable system for monitoring adverse events; adequate labeling for warnings and contraindications; consumer education; recognition that ephedra use for weight loss and ergogenic purposes constitutes treatment for a health condition (not a dietary supplement structure/function role); long-term trials to establish dose levels and duration guidelines; good manufacturing practices; and a research agenda.¹⁰

On June 14, 2002, the HHS Secretary Tommy Thompson announced new efforts to expand scientific research on the safety of ephedrine alkaloids and aggressively pursue the illegal marketing of non-herbal synthetic ephedrine alkaloid products.¹¹ On October 7, 2002, FDA stopped imports of the ephedra-containing products by the Dutch operator selling these products in the United States. In addition, the agency sent inspectors to the New Jersey firm that was distributing the Dutch-made products in this country. When inspectors were denied access to the building, a court order was obtained to enter the building and inspect the company's records. On October 8, 2002, Secretary Thompson announced that he had asked FDA to evaluate the best scientific evidence available and recommend the strongest possible mandatory warning labeling for ephedra-containing products.

Following the deaths of several athletes, FDA reopened for 30 days its earlier proposed rules for ephedra on March 5, 2003. The published document specifically requested comments on the portions of the proposal that addressed dosing, labeling and warning statements, based on new evidence concerning health risks associated with the use of supplements containing ephedrine alkaloids. In addition, the agency signaled its intention to consider whether in light of recent evidence it should determine that ephedra-containing supplements present a "significant or unreasonable risk of illness or injury under conditions of use recommended or suggested in labeling." FDA also sought comments on whether additional legislative authorities would be necessary or appropriate to enable it to address this issue most effectively. The agency had proposed the following warning statement to appear on the principal display panel of the supplement product (**see Box 1**). The additional information provided in **Box 2** was to appear on the outer product label or in product labeling that is an integral part of the outer product packaging, such as information at the point of purchase.

¹⁰ Jones, W. *Safety of Dietary Supplements Containing Ephedrine Alkaloids*. Public Meeting Aug. 8-9, 2000. Report. 5 p.

¹¹ U.S. Department of Health and Human Services. HHS Announces Plans To Study Ephedra; Steps Up Enforcement of Illegal Ephedrine Marketing. HHS News. June 14, 2002. [<http://www.hhs.gov/news/press/2002pres/20020614.htm>]

On December 30, 2003, HHS and FDA announced plans to prohibit the sale of dietary supplements containing ephedra. The ban will take effect 60 days after the final rule is published. In the meantime, FDA has released a consumer alert that announces its plan to prohibit sales of ephedra-containing dietary

Box 1. Proposed Warning Label for Principal Display Panel

Warning: Contains ephedrine alkaloids. Heart attack, stroke, seizure, and death have been reported after consumption of ephedrine alkaloids. Not for pregnant or breast-feeding women or persons under 18. Risk of injury can increase with dose or if used during strenuous exercise or with other products containing stimulants (including caffeine). Do not use with certain medications

supplements and urged consumers to stop using these products. The agency also sent certified letters to over 60 manufacturers who had been producing supplements containing ephedra to provide the companies with advance notice of the final rule to be published to facilitate their earliest compliance. The 60-day period following publication of the final rule is required under the Congressional Review Act. The decision to prohibit the sale of ephedra under the safety provisions of DSHEA represents the first time that the statute has been used to remove a supplement ingredient from the marketplace.

In its announcement of its plans to prohibit the sale of ephedra-containing supplements, the Department indicated that it had reached this decision after conducting an exhaustive and highly resource-intensive process that is required under the provisions of DSHEA for banning a supplement that presents a significant and unreasonable risk to human health. To meet the safety standard, FDA gathered and thoroughly reviewed a prodigious amount of evidence about ephedra's pharmacology, clinical studies of ephedra's safety and effectiveness, newly available adverse events reports, the published literature, and a seminal report by the RAND Corporation. The agency also reviewed tens of thousands of public comments on its February 2003 request for information about ephedra-associated health risks. Coupled with several high-profile deaths alleged to be from ephedra use and the subsequent reopening of the comment period on the previously-published proposed rule on ephedra regulation plus increasing pressure from Congress, the agency's decision is the culmination of a process that began in 1997 when FDA first proposed to require warning statements on the hazards of ephedra use.

Since the announcement on the ephedra ban, the agency has also indicated that it plans to move beyond its recent action against ephedra and increase its focus on certain other supplements. The FDA commissioner recently indicated the agency's intention to examine bitter orange, aristolochic acid and usnic acid, which are ingredients of weight loss products. These three supplement ingredients have been associated with kidney and liver problems.

Box 2. Proposed Additional Information for Product Labeling

This product contains ephedrine alkaloids, which can have potentially dangerous effects on the heart and central nervous system.

Do not use with

- ✓ a monoamine oxidase inhibitor (MAOI) or for 2 week after stopping a MAOI drug;
- ✓ certain drugs for depression, psychiatric, or emotional conditions;
- ✓ drugs for Parkinson's disease;
- ✓ drugs for obesity or weight control;
- ✓ methyldopa.

Contact a doctor before using this product if you have or ever had

- ✓ heart disease, high blood pressure, thyroid disease, seizure, diabetes, depression, and other mental, emotional or behavioral conditions, glaucoma, or difficulty urinating due to prostate enlargement.

Stop use and contact a doctor immediately if these side-effects occur

- ✓ dizziness, severe headache, rapid and/or irregular heartbeat, chest pain, shortness of breath, nausea, loss of consciousness, or changes in emotions or behavior (such as depression, hallucinations or severe mood swings).

Your risks of serious side-effects from this product can increase

- ✓ with increased dose, frequency, or duration of use;
- ✓ if you take it with other dietary supplements containing ephedrine alkaloids (such as ephedra, ma huang, Sida cordifolia);
- ✓ if you take it with additional products containing stimulants, such as carfeinated beverages and foods (including dietary supplements containing guarana, kola nut, mate yohimbine/yohimbe, Citrus aurantium);
- ✓ if you take it with medications synephrine, phenylephrine, ephedrine, pseudoephedrine, or phenylpropanolamine;
- ✓ if you use it before or during strenuous exercise.

Congressional Attention

During a 1999 hearing of the House Committee on Government Reform, the limitations of FDA's current adverse events reporting system were scrutinized.¹² The agency acknowledged that all adverse event reporting cases were posted on its website without being subjected to a vetting process to determine the likely cause of the adverse reaction. According to FDA officials, this process was used to expedite release of adverse cases to interested parties, in lieu of freedom of information procedures which usually take up to a year to respond to specific requests. Thus, the cases are reported as they are received due to the agency's limited resources to review the cases before they are released. Committee members acknowledged that the resources needed to improve the adverse events reporting system were limited.

¹² U.S. House of Representatives. Committee on Government Reform. *How Accurate is the FDA's Monitoring of Supplements Like Ephedra?* 106th Cong., 1st sess. Comm. Print. 106-60. May 27, 1999. 89 p.

The House Committee on Science requested that the General Accounting Office (GAO) examine the scientific basis for FDA's ephedra supplement proposal and determine whether the agency adhered to the regulatory flexibility analysis requirements for federal rulemaking. On August 4, 1999, GAO released a report in which it raised concerns about the process by which FDA had compiled the 800 reports on the harmful effects of ephedra.¹³ The report indicated that the agency was justified in its determination that the number of adverse events relating to supplements containing ephedra warranted agency attention and consideration of steps to address safety concerns. However, GAO expressed concern about the manner in which FDA used the adverse events reports in supporting the proposed dosing levels and duration of use limits, and concluded that the agency needed additional evidence to support these restrictions. The report indicated that while ephedra might be harmful, the agency lacked adequate data to set dosage levels. GAO concluded that FDA's economic analysis contained the basic elements of a federal agency's cost-benefit analysis; however, the agency analysis was not sufficiently transparent about how it reached its estimate of the costs and benefits of the proposed actions.

In the FY2001 HHS appropriations report (S.Rept. 106-293 accompanying S. 2553), the Senate Committee on Appropriations indicated its continued support for the work of the Office of Dietary Supplements (ODS) at the National Institutes of Health (NIH) and the need for additional research to better inform consumers of the health benefits of supplements. The Committee specifically encouraged ODS to support research on ephedra within the funds provided.

On October 9, 2001, Representative Susan Davis introduced the Ephedrine Alkaloid Consumer Protection Act (H.R. 3066), the first bill to specifically address this dietary supplement ingredient. The bill would have required that supplements containing ephedrine alkaloids be labeled with a warning against use by individuals under 18 years of age, and during pregnancy or nursing. The label would also have directed users to consult a physician before use, if an individual had a personal or family history of a number of health conditions, or if certain drugs or dietary supplement ingredients were being used. The label would also have required a statement that consuming the product might cause adverse health effects, and recommended discontinuing use and contacting a health professional immediately, if certain severe side effects occurred. Labeling would have warned about use of the products when additional caffeine was being consumed, and would have required disclosure of the number of milligrams of ephedrine alkaloids and any other stimulant present in a serving, standardized nomenclature for the ephedrine ingredient, provided a toll-free number and internet address maintained by the Secretary of HHS for reporting adverse effects, a labeling and advertising warning that ephedrine alkaloids were present in the product which may cause adverse health effects and directed the user to read the label and follow directions. The bill would have also prohibited the sale to anyone under the age of 18 years and required ephedrine alkaloid-containing products to be behind the counter in retail

¹³ U.S. General Accounting Office. Dietary Supplements: *Uncertainties in Analyses Underlying FDA's Proposed Rule on Ephedrine Alkaloids*. GAO/HEHS/GGD-99-90. July 1999. 79 p.

establishments. The bill was referred to the House Committee on Energy and Commerce and no additional action occurred.

Several hearings were held in 2002. On July 25, the House Committee on Government Reform convened a hearing on the recent research on the impact of diet and lifestyle on personal health, the growing trend toward obesity and the use of supplements in promoting good health. The draft RAND Corporation report that reviews the literature on health problems associated with ephedra was discussed during the hearing. Subsequently, the Committee requested that GAO review health-related calls that one company collected from consumers from May 1997 to July 2002. GAO examined the extent to which consumer information in the records was comprehensive, interpretable and consistently recorded, counted the number of call records reporting types of adverse events that FDA had identified in 1997 as serious or potentially serious, and compared its findings with those of six other reviews of the call records, including one by the company.¹⁴ GAO reported in March 2003 that it counted 96 reports that were for heart attacks, strokes, seizures, deaths and cardiac arrest. The company had identified 78 cases, the other reviews had ranged from 65 to 107 cases.

On July 31, 2002, the Senate Committee on Governmental Affairs' Subcommittee on Government Management, Restructuring and the District of Columbia held a hearing entitled "When Diets Turn Deadly: Consumer Safety and Weight Loss Supplements," which focused on ephedra-containing supplements and the current evidence linking them to serious health problems. Subsequently the subcommittee convened a hearing on October 8, following the death attributed to ephedra of a 16-year-old athlete in the Chairman's district. The hearing focused on the illegal marketing of products containing ephedra to individuals, particularly athletes, in certain age groups. A general consensus of the witnesses was that availability of these products should be restricted for individuals under 18 years of age.

In the 108th Congress, several resolutions and bills that specifically address ephedra/ephedrine alkaloids have been introduced. H.Con.Res. 52 as introduced by Representative Hooley on February 25, 2003, expresses the sense of Congress that all major sports organizations should ban the use of ephedra and dietary supplements containing ephedrine. Currently the National Football League, the National Collegiate Athletic Association, the International Federation of Football Associations and the International Olympic Committee have banned use of ephedra and supplements containing ephedrine. H.Res. 435 was introduced by Representative Davis on November 6, 2003. It expresses the sense of the House of Representatives that the Secretary of Health and Human Services should take immediate action to remove dietary supplements containing ephedrine alkaloids from the market. Both resolutions were referred to the Committee on Energy and Commerce and subsequently to the Subcommittee on Health, but no further action has been taken. S.Res. 260 was introduced by Senator Durbin on November 6, 2003. It expresses the sense of the Senate that the Secretary of Health and Human Services should take

¹⁴ U.S. General Accounting Office. Dietary Supplements *Review of Health-related Call Records for Users of Metabolife* 356. GAO-03-494. March 2003. 31 p.

action to remove dietary supplements containing ephedrine alkaloids from the market. It was referred to the Committee on Health, Education, Labor, and Pensions, but no further action has been taken.

H.R. 725 was introduced by Representative Susan Davis to amend the Federal Food, Drug and Cosmetic Act to establish labeling and advertising requirements for dietary supplements containing ephedrine alkaloids and prohibit sales to individuals under 18 years of age. The bill would require warning statements and dosage information similar to that proposed by FDA as well as contact information for purposes of the medical product reporting program. In addition to the prohibition of sales to minors, the bill would require that products be held in a portion of the retail establishment not intended to be accessible to its customers. These provisions are similar to the bill introduced in the 107th Congress. The bill was referred to the House Committee on Energy and Commerce and subsequently to the Subcommittee on Health, but no further action has occurred.

On March 4, 2003, H.R. 1025 was introduced by Representative Sweeney, which is entitled the Ephedra Public Protection Act. It would require premarket approval for supplements containing ephedrine group alkaloids and subsequent reporting of serious adverse effects once they were allowed to be marketed. The bill defines 'ephedrine supplements,' 'serious adverse experiences' and 'documented incident.' The bill would also require that the Secretary of HHS publish the proposed rules of good manufacturing practices with 120 days of enactment. (The proposed rules for good manufacturing practices for dietary supplements were actually published on March 13, 2003). Finally, the bill would require the testing of each production lot/batch of ephedrine containing product to ensure label accuracy and carry an expiration date on the label. The bill was referred to the House Committee on Energy and Commerce and subsequently to the Subcommittee on Health, but no further action has yet occurred.

Several days of hearings were convened in 2003. The House Committee on Energy and Commerce held a two-day hearing on issues related to ephedra containing dietary supplements.¹⁵ On the first day, witnesses included victims' families, researchers, several manufacturers, and agency officials. The second day the witnesses included representatives of collegiate and major league sports: baseball, auto racing, football, and soccer. At a hearing convened by the Senate Committee on Commerce, Science, and Transportation on October 28, 2003, the Members heard testimony from representatives of the FDA, the Federal Trade Commission, Anti-Doping Agency, a supplement trade association, consumers, and a scientist. The hearing was designed to determine the availability of supplements to consumers of all ages, industry marketing practices, the effectiveness of DSHEA to protect consumers and whether the current level of domestic consumption exposes consumers to unexpected long- and short-terms effects.

¹⁵ House of Representatives. Committee on Energy and Commerce. Subcommittee on Oversight and Investigations, and Commerce, Trade and Protection. Hearings. Issues Relating to Ephedra-Containing Dietary Supplements. July 23 and 24, 2003. 108th Congress, 1st session. Serial no. 108-43. 270 p.

Published Research

On November 6, 2000, the New England Journal of Medicine released an article on the health effects of dietary supplements containing ephedra.¹⁶ The report was the result of an FDA request for an independent review of adverse event reports related to the use of supplements containing ephedra to assess causation, and to estimate the level of risk that use of these supplements poses to consumers. The researchers reviewed 140 reports of adverse events related to ephedra-containing supplements submitted to FDA between June 1, 1997 and March 31, 1999. The results indicated that 31% of cases were considered to be definitely or probably related to the use of ephedra-containing supplements and 31% were deemed to be possibly related. Among the adverse events, 47% involved cardiovascular symptoms (hypertension, palpitations, tachycardia and stroke) and 18% involved the central nervous system (seizures). Ten events resulted in deaths and 13 events produced permanent disability. The authors concluded that the use of ephedra-containing dietary supplements may pose a health risk to some individuals and the findings indicate the need for a better understanding of individual susceptibility to the adverse effects of these supplements. The final version of the report was published in NEJM on December 21, 2000.¹⁷ The early release of the article was a decision of the editors because of the potential public health significance of the study results.

Researchers at several institutions recently conducted a 6-month clinical trial to assess the safety and efficacy for weight loss of an herbal supplement containing Ma Huang and caffeine.¹⁸ They concluded that herbal ephedra and caffeine lowered body weight, fat and BMI (basal metabolic index). Blood pressure was transiently and heart rate persistently increased, but cardiac arrhythmias were not increased. Self-reported symptoms were similar to those for synthetic ephedrine and caffeine products.

A recent report on the use of herbal medicines prior to surgery suggests that certain products may increase the risk of morbidity and mortality.¹⁹ Researchers at the University of Chicago identified eight herbs (including ephedra) that potentially pose the greatest hazard to care of patients undergoing surgery. The study found that, for ephedra, the relevant pharmacological effects included increased heart rate and blood pressure, which increased the risk for heart attack and stroke. Use of the supplement needed to be discontinued at least 24 hours before surgery. The report concluded by suggesting that during the preoperative evaluation, physicians need to

¹⁶ Haller, C. A., and N. L. Benowitz. *Adverse Cardiovascular and Central Nervous System Events Associated with Dietary Supplements Containing Ephedra Alkaloids*. New England Journal of Medicine. Nov. 6, 2000.

¹⁷ Haller, C. A., and N. L. Benowitz. *Adverse Cardiovascular and Central Nervous System Events Associated with Dietary Supplements Containing Ephedra Alkaloids*. New England Journal of Medicine. v. 343, no. 25, Dec. 21, 2000. p 1833-1838.

¹⁸ Boozer, C. N., et al. *Herbal Ephedra/Caffeine for Weight Loss: A 6 Month Safety and Efficacy Trial*. Obesity Research v. 9, no 1. 2001. p. 68.

¹⁹ Ang-lee, M, J. Moss and C. Yuan. *Herbal Medicines and Perioperative Care*. Journal of American Medical Association. July 11, 2001. v. 286, no. 2, p. 208- 216.

explicitly elicit and document a history of herbal medication use, as well as learn the potential preoperative effects of the commonly used herbal medications to prevent, recognize and treat potentially serious problems associated with their use and discontinuation.

A separate analysis of adverse reactions to ephedra and other herbal products during 2001 documented by the Toxic Event Surveillance System was published.²⁰ Products containing ephedra alone or in combination with other herbs or substances accounted for 64% of all adverse reactions, while these products represented only 0.82% of herbal products sales. The relative risk for an adverse reaction from ephedra was markedly elevated in comparison to all other individual herbs by 10- to 40-fold.

NIH – Office of Dietary Supplements

In January 2002, the congressionally mandated Office of Dietary Supplements (ODS) at the National Institutes of Health and the Council for Responsible Nutrition convened a 2-day conference on the science and policy aspects of performance-enhancing supplement ingredients, such as ephedra, androstenedione and creatine. The sessions reviewed the scientific evidence on the benefits and risks of certain supplements in performance enhancement, and the challenges facing regulators, educators and sport health professionals in working with individuals consuming these products.

ODS initiated a systematic review of the literature on ephedra through the Agency for Healthcare Research and Quality (AHRQ), which conducted the analysis in its Evidence-based Practice Center at its RAND-Southern California unit. The review addressed a series of questions related to safety and efficacy of ephedra, alone and in combination with other ingredients, for use in weight management, athletic performance and energy enhancement. The reviewers concluded that ephedrine and ephedra promote a modest short-term weight loss in clinical trials.²¹ They determined that there were no data on long-term weight loss, and insufficient evidence to support the use of ephedra for athletic performance. The evidence did show that the use of ephedra or ephedrine with caffeine was associated with increased risk of psychiatric, autonomic or gastrointestinal symptoms, and heart palpitations. The report will be used to assist in shaping the ODS research agenda related to ephedra.

Health Canada

On June 14, 2001, Health Canada (HC) released an advisory, warning consumers not to use products that contain ephedra, either alone or in combination with caffeine and other stimulants, for weight loss, body building or increased

²⁰ Bent, S. et al. *The Relative Safety of Ephedra Compared with Other Herbal Products*. *Annals of Internal Medicine*. v.138, no.6. Mar. 18, 2003. p.468-471.

²¹ Shekelle, P.G. et al. *Efficacy and Safety of Ephedra and Ephedrine for Weight Loss and Athletic Performance*. *Journal of the American Medical Association*. v. 289, no.12, Mar. 26, 2003 p. 1537-1545.

energy.²² The agency noted that it has authorized ephedrine only for use in nasal decongestants in OTC cold products. Its last action was about 3 years earlier when it addressed Ma Huang use in diet aids. Health Canada had been contemplating issuing the advisory for some time, based on its review of FDA's AER database and 60 AERs, two of which were deaths, related to ephedra use in Canada before October 2000.

In January 2002, Health Canada banned the distribution, sale and/or importation of all ephedra-containing products that had a unit dose of more than 8 milligrams (mg) of ephedra or 32 mg per day, and combination products containing ephedra with other stimulants (such as caffeine). It also banned ephedra products with labeled or implied claims for appetite suppression, weight loss promotion, metabolic enhancement, increased exercise tolerance, body-building effect, euphoria, increased energy or wakefulness or other stimulant effects. Products were to be recalled to the retail level and retailers were to remove the product from store shelves and return them to their suppliers. Health Canada issued this ban under a Class I Health Hazard for a high-risk population (individuals who suffer from certain pre-existing chronic conditions) and a Class II Health Hazard for the general population. Products containing ephedra, which are marketed for traditional medicine, will continue to be available, provided that they do not contain caffeine or exceed the ephedra content of 8 mg per dose to a maximum of 32 mg per day. Products with drug identification numbers that are sold as nasal decongestants and meet the same dose levels will also continue to be available. Health Canada plans to continue to monitor reports of adverse events associated with ephedra and will take further action as necessary. A random market survey was to be conducted within 6 months of the requested recall to determine whether these products have remained off the Canadian market.

State Regulation of Ephedra

In the absence of FDA regulation of dietary supplements containing ephedra, a number of states have attempted to take action to regulate ephedra following reported adverse effects on consumers. State efforts have taken several different forms. Some states have regulated the product by age group, some states have declared it an illegal drug, while other states have adopted regulations on how and to whom it can be sold. See the CRS Congressional Distribution memorandum entitled *Ephedrine: Federal and State Law Regarding Access and Control*, by M. Ann Wolfe and Diana T. Duffy, November 2, 2000, for further information on state action.

In March 2003, Suffolk County, New York banned the sale of ephedra; in April, the New York City Council introduced a bill to ban ephedra sales as well. Subsequently the State of New York banned ephedra sales and California followed suit. Illinois legislation banning the sale of ephedra was signed into law on May 25, 2003, following the death of a 16-year-old high school athlete.

²² *Ephedra in Canada*. The Tan Sheet. June 25, 2001. p. 32.

Industry Self-Regulation

Since 1994, the major trade associations representing manufacturers of the dietary supplement industry (the American Herbal Products Association-AHPA, the Consumer Healthcare Products Association-CHPA, the Council for Responsible Nutrition-CRN, the National Nutritional Foods Association-NNFA, and the Utah Natural Products Association-UNPA) have participated in a voluntary program for the formulation and labeling of ephedra-containing products. In many respects, the voluntary program addresses the same issues that were included in the provisions of FDA's proposed rule. The industry's self-regulation provisions were based on the OTC drug standards for ephedrine.

Under the provisions of the voluntary program, a limit on serving size for products containing ephedra is not to exceed 25 mg, for a total of not more than 100 mg per day. Product labeling is required to be in conformity with the standard common name listed in the *Herbs of Commerce*.²³ A listing of the amount of ephedra per serving is required on the label. No synthetically derived ephedrine or their salts are allowed either in the finished product or in raw materials used in their manufacture. Claims that the product may be useful to achieve an altered state of consciousness, euphoria or as a "legal" street drug are not permitted. A label statement including the following information or a statement in conformance with applicable OTC drug monographs must be included:

- Not intended for use by anyone under the age of 18;
- Do not use this product if you are pregnant or nursing;
- Consult a health care professional before using this product if you have heart disease, thyroid disease, diabetes, high blood pressure, a psychiatric condition, difficulty in urinating, prostate enlargement or seizure disorder, if you take monoamine oxidase inhibitor (MAOI) or any other prescription drug, or you are using an over-the-counter drug containing ephedrine, pseudoephedrine or phenylpropanolamine (ingredients found in certain allergy, asthma, cough/cold and weight control products);
- Exceeding recommended serving will not improve results and may cause serious adverse health effects; and
- Discontinue use and call a health care professional immediately, if you experience rapid heart beat, dizziness, severe headache, shortness of breath or other similar symptoms.

Several states have considered, and four (Ohio, Washington, Hawaii and Michigan) have already implemented, adoption of the industry's voluntary standards as their requirements for herbal ephedra products. In May 1999, the supplement industry suggested that FDA adopt the industry's standards either as industry

²³ American Herbal Products Association. *Herbs of Commerce*. Austin, Texas, 1992. 78 p. (A compilation of common names of herbs standardized to botanical names in order to reduce nomenclature problems for trade purposes.)

guidance or the basis for developing a regulation.²⁴ More recently, CHPA has recommended that FDA adopt the industry program standards into regulation.²⁵

On October 25, 2000 a citizen's petition on ephedra was filed with FDA by four trade associations (AHPA, CHPA, NNFA, and UNPA).²⁶ The petition requested that the agency revoke the parts of the 1997 proposed ephedra rule that still stand and implement an industry standard for the labeling and marketing of dietary supplements containing ephedra. The industry standard for labeling and marketing of supplements containing ephedra outlined in the petition are essentially the same as the provisions (outlined above in this report) of the industry's voluntary program that has been in place for more than 8 years. The industry indicated in the petition that virtually all major manufacturers and distributors of ephedra products (represented by the trade associations filing the petition) have already adopted the voluntary program guidelines.

In December 2000, the Council for Responsible Nutrition announced the results of the Cantox Health Sciences International Report that it had funded to review recent clinical trials on the safe use of ephedra.²⁷ Cantox analyzed in detail 19 clinical trials, AERs from FDA, case reports and published articles, including data from human and animal studies. The report indicated that ephedra is safe to use at a total daily dose of 90 mg, divided into smaller doses of up to 30 mg each, which would cause no observed adverse effects. In addition, a 150 mg total daily dosage was determined to be the lowest level at which moderate adverse effects were first observed.

Observations

The determination by HHS and FDA that ephedra is a risk to public health under the standard for safety in DSHEA represents the first time that the 1994 statute has been used to prohibit the sale of a dietary supplement. The process, which started in 1997, was both time consuming and labor intensive on the part of the Department to establish that it had met the standard of significant and unreasonable risk. The final decision appears to have been based on the collective information available: ephedra's pharmacology, clinical studies of its safety and effectiveness, hundreds of adverse event reports, an extensive review of the published literature, and a report of an independent scientific institute. Assuming that the Department's decision stands up to any challenges that may occur, the ephedra case may serve as a model for the

²⁴ McGuffin, M. American Herbal Products Association. Statement. Presented at the Safety of Dietary Supplements Containing Ephedrine Alkaloids Public Meeting. Aug. 8-9, 2000. 5 p.

²⁵ Soller, R. W. Consumer Healthcare Products Association. Comments on the safety evaluation of ephedra. Presented at the Safety of Dietary Supplements Containing Ephedrine Alkaloids Public Meeting. Aug. 8-9, 2000. 5p.

²⁶ APHA, CHPA, NNFA, UNPA. Citizen's Petition to the Food and Drug Administration on Dietary Supplements Containing Ephedrine Alkaloids. Oct. 25, 2000. 6 p.

²⁷ Cantox Health Sciences International. *Safety Assessment and Determination of a Tolerable Upper Limit for Ephedra*. Dec. 20, 2000.

review process and procedures for a supplement that raises public health concern in the future.

The current voluntary adverse reporting system continues to be controversial due to its limitations in providing the information needed to determine causality between the use of supplements containing ephedra and suspected health problems. These limitations have also made it difficult for FDA in its rulemaking to address safety, duration of use and dosage levels for dietary supplements containing ephedra. The AER reports are generally incomplete and difficult to use in establishing whether ephedra was the “cause” of a particular adverse event in a given individual. Furthermore, according to Barnes et al.,²⁸ the number of adverse reports received into the system may represent an under-reporting of the actual number of adverse events occurring. Future additional research on the use of ephedra for weight reduction may shed some light on its efficacy as well as on any adverse events that may occur in a more controlled research environment and holds out the possibility of evidence of benefits outweighing the risks to the extent that it might be regulated and used as a drug. Congress has also reviewed the problems with the voluntary AERs system for supplements in several hearings and reports and may consider a different means of reporting adverse events for supplements.

Nevertheless, the number of adverse event reports relating to supplements containing ephedra seems to indicate that there is a problem with its use in at least a select group of consumers who experience severe adverse reactions, including life-threatening events, following use of the supplements. Given the current dearth of controlled clinical trials, it is impossible to ascertain which consumers, many of whom seem to have no known health problems, might be adversely affected by ephedra use. It seems plausible that determining a safe level of ephedra for the general population as a whole may never be possible. In April 2003 the American Heart Association urged a total ban on over-the-counter ephedra sales. The announcement of FDA’s decision to prohibit the sale of supplements containing ephedra signals that a final regulation is forthcoming based on the agency’s determination at least for now that there is no safe level. However, the final rule will still be subject to the Congressional Review Act, which could alter the final language of the rule.

The congressional language encouraging NIH-ODS to conduct research on ephedra was aimed at helping to generate the answers to numerous questions on the health effects and the vulnerable populations that should avoid use of this supplement. However, no specific funding has been provided for such an initiative; Congress has indicated that it should be supported out of existing funds. While the funding provided to ODS has been increased in recent fiscal years, there are a number of areas of research investigation competing for the monies that the office receives. Furthermore, the results of any research focused on a specific supplement ingredient that is funded by NIH-ODS will not be available for 3-5 years because of the time involved in initiating such a program, completion of the research, and publication of

²⁸ Barnes, J., et al. *Different Standards for Reporting ADRS to Herbal Remedies and Conventional Otc Medicines: Face-to-face Interviews with 515 Users of Herbal Remedies*. *Journal of Clinical Pharmacology*. v. 45, 1998. p. 496-500.

the results in a peer-reviewed journal. Nevertheless, the recent announcement concerning the expansion of research on the safety of these products suggests that the Department recognized the need to seek additional information on the health impact from the use of ephedra-containing supplements. The plans for future research on supplement ingredients may be influenced by the FDA's decision to further examine specific ingredients in dietary supplement products that in its opinion represent potential health problems.

Given the recent high profile deaths associated with ephedra and the amount of controversy surrounding the strict requirements that FDA proposed for dietary supplements containing EA, it will be interesting to see the language of the final rules compared to the original proposed rule. The more moderate voluntary self-regulatory program for the formulation and labeling of ephedra-containing products that the supplement industry has had in place for some time was not adopted by all manufacturers of ephedra-containing products. Bills introduced in the 108th Congress would mandate a number of the provisions of both the FDA proposed rules and the self-regulatory program that the supplement industry has endorsed. Resolution of the regulatory stalemate may have been resolved by the FDA decision to prohibit the sale of this supplement ingredient for now. However, the long-term impact of the ephedra ban may be to raise concern among some lawmakers and others about changes that some believe are needed to make DSHEA more effective in addressing problems in the future.