**STATEMENT**
**for the Record**
**of the**
**American Medical Association**
**to the**
**Subcommittee on Oversight of Government Management, Restructuring**
**and the District of Columbia**
**Committee on Government Affairs**
**United States Senate**

## RE: DANGERS OF DIETARY SUPPLEMENT EPHEDRA

**October 8, 2002**

Good morning Chairman Durbin and members of the Subcommittee. I am Ron Davis, MD, a member of the Board of Trustees of the American Medical Association (AMA). I am pleased to be able to testify today on behalf of the AMA. As a preventive medicine physician, I serve as director of the Center for Health Promotion and Disease Prevention at the Henry Ford Health System in Detroit, Michigan.

The physician members of the AMA are very concerned about the quality, safety, and efficacy of dietary supplement products, especially herbal (botanical) products, and we commend Chairman Durbin and this Subcommittee for their continued focus on this problem. I would like to begin this testimony with a series of questions.

- Do dietary supplement products actually contain the active ingredient(s) (and strength[s]) that their manufacturers claim on the labeling?
- Are these products really as safe as the promotional materials of the manufacturers claim them to be?
- Does the degree of safety change in individuals who have pre-existing diseases and conditions, or in those individuals who are also taking prescription medications?
- Are the structure/function claims for these products accurate and based on good science?
- Are these products being used inappropriately to treat diseases or potentially delaying individuals with diseases from obtaining effective care that may include prescription medications?

The AMA does not believe that satisfactory answers to these questions have been offered to either public health officials or the general public. Because dietary supplements are classified as foods rather than drugs, rigorous safety and efficacy standards are not required for these products. Also, standards for product quality and for Good Manufacturing Practices (GMP) do not yet exist.

The primary obstacle to effective regulation in this area is the Dietary Supplement Health and Education Act of 1994 (DSHEA), which fails to provide for adequate Food and Drug Administration (FDA) regulatory oversight of dietary supplements. The AMA has urged Congress to amend DSHEA to require that dietary supplements, including those products already in the marketplace, undergo FDA approval for evidence of safety and efficacy; meet standards established by the United States Pharmacopoeia (USP) for identity, strength, quality, purity, packaging, and labeling; and meet FDA postmarketing requirements to report adverse events, including drug interactions.

The AMA commends the HHS Office of Inspector General (OIG) for its report entitled, “Adverse Event Reporting for Dietary Supplements: An Inadequate Safety Valve,” that found the current regulatory system for dietary supplements to be substantially inadequate. The AMA supports the OIG’s recommendations to strengthen the standards to which dietary supplements are subject.

In the absence of modifications to the current federal law, the FDA must aggressively regulate dietary supplements to the fullest extent possible, to fulfill its obligation to protect the health of the American public. The AMA has expressed this

view to the FDA on numerous occasions through letters to the Commissioner and to various FDA Dockets.

Because dietary supplements are classified as foods under federal law, they are assumed to be safe and are subject to limited regulatory oversight. Therefore, it is imperative that dietary supplement products have essentially no risks, i.e., they must be extremely safe, and provide some benefits for consumers. As discussed below, the AMA believes that dietary supplement products containing ephedrine alkaloids fail to satisfy this requirement for a high benefit/risk ratio.

As requested, the AMA has structured its statement to respond to the six questions posed by the Subcommittee.

*Question 1. Why has the AMA asked the FDA to initiate proceedings to remove dietary supplement products containing ephedrine alkaloids from the United States market?*

In letters dated September 28, 2000, and January 28, 2002, the AMA encouraged the FDA to initiate proceedings to remove dietary supplements containing ephedrine alkaloids from the United States market. The AMA believes the FDA has sufficient cause to take this action under Section 402(f)(1)(A)(i) of the Federal Food, Drug, and Cosmetic Act (FDCA). Specifically, these products should be deemed adulterated because they present a significant or unreasonable risk of illness or injury under conditions of use recommended or suggested in the labeling. Unfortunately, the Agency has failed to acknowledge or respond to the AMA's comments.

The AMA has taken this position based on a number of considerations:

a. Over 1,000 voluntarily submitted Adverse Event Reports (AERs) associated with dietary supplements containing ephedrine alkaloids have been received by the FDA. A number of these AERs have described events that have resulted in death or serious morbidity (e.g., cardiac arrhythmias, myocardial infarctions, seizures and strokes). Many of these AERs were for young, presumably healthy, adults. Additionally, a subset of individuals may develop drug-seeking behavior or dependence on ephedra-containing products. Due to the nature of voluntary patient safety reporting systems, these AERs underestimate the actual number of adverse events that have occurred. As noted in the Subcommittee's invitation to appear, one company alone recently admitted to having received, since 1995, more than 14,000 AERs associated with dietary supplements containing ephedrine alkaloids.

b. In August 1996, after reviewing approximately 800 AERs and other evidence, a majority of the members of FDA's Food Advisory Committee stated that, "based on the available data, no safe level of ephedrine alkaloids could be identified for use in dietary supplements." It recommended that FDA remove dietary supplements containing ephedrine alkaloids from the market. However, the FDA did not take this advice.

c. Similarly, in 2000, four outside experts (two in clinical pharmacology and one each in psychopharmacology and neurology) commissioned by the FDA to review 140 new AERs concluded that a number of serious adverse events, including deaths, were most likely due to ephedrine alkaloids in dietary supplements. Three of these experts believed that dietary supplements containing ephedrine alkaloids posed a significant and unreasonable risk.

d. The AMA recognizes that it is difficult to prove cause-and-effect relationships based on voluntary AERs. Nonetheless, the primary question that should be considered by the FDA is whether manufacturers' claims of purported benefits for these products outweigh the products' risks. We continue to believe that the benefits do not outweigh the risks, and the weight of the available clinical evidence supports the removal of dietary supplement products containing ephedrine alkaloids from the market. Purported uses for these products include weight loss, energy enhancement, enhancement of athletic performance, body building, and euphoria. The AMA strongly believes that, with the possible exception of weight loss, the other purported uses of dietary supplements containing ephedrine alkaloids are of questionable benefit. Moreover, the AMA is unaware of any well-controlled clinical trials that prove efficacy for these purported uses. Taking into account the high number of AERs and the extremely questionable uses of ephedrine alkaloid-containing products, the AMA believes the benefit/risk ratio for these products is unacceptable.

e. Obesity is a significant public health problem in the United States. However, the AMA's position is that obesity should be categorized as a disease whose management should include dietary modification, exercise, and, when

indicated, drug therapy. A number of prescription drugs, including phentermine, phendimetrazine, orlistat, and sibutramine, are available to treat obesity in the United States. In addition, surgical procedures can be used to treat morbid obesity. In Denmark, ephedrine alkaloids are available to treat obesity, but these products can be obtained only by prescription. Interestingly, phenylpropanolamine, one of the active constituents in ephedrine alkaloids, recently was withdrawn as an over-the-counter drug for appetite suppression (also as a decongestant) from the U.S. market because it was associated with an increased risk of hemorrhagic stroke.

f. National Institutes of Health (NIH) guidelines for the treatment of obesity state that herbal preparations, including ephedra-containing products, are not recommended as part of a weight-loss program.

g. Recently, Health Canada, the Canadian agency with FDA-like authority, requested a recall of many *Ephedra*/ephedrine-containing products from the market because such products pose a serious risk to health. Specifically, Health Canada recalled:

- *ephedra*/ephedrine products with a dose unit of more than 8 mg of ephedrine, or a label recommending more than 8 mg/dose or 32 mg/day, and/or a labeled or implied use exceeding 7 days;
- all combination products containing *Ephedra*/ephedrine together with stimulants (e.g., caffeine) and other ingredients which might increase the effect of *Ephedra*/ephedrine in the body; and
- *ephedra*/ephedrine products with labeled or implied claims for appetite suppression, weight-loss promotion, metabolic enhancement, increased exercise tolerance, body-building effects, euphoria, increased energy or wakefulness, or other stimulant effects.

In conclusion, the AMA encourages the FDA to initiate proceedings to remove dietary supplements containing ephedrine alkaloids from the United States market because the risks associated with the use of these products outweigh the benefits.

*Question 2. Do ephedrine alkaloids pose the same risk for hemorrhagic stroke as phenylpropanolamine (PPA)?*

Ephedrine alkaloids are sympathomimetic amines that affect the cardiovascular system by increasing blood pressure and heart rate. Ephedrine also is a central nervous system (CNS) stimulant. Based on the voluntary AERs reported to the FDA, the most serious adverse events associated with ephedrine alkaloids have been those that would be expected of potent sympathomimetic amines, including cardiac arrhythmias, myocardial infarctions, sudden death, strokes, and seizures.

Phenylpropanolamine (PPA) is a *synthetic* sympathomimetic amine that was used in numerous over-the-counter (OTC) medications as a decongestant and for weight loss. Recently, PPA was withdrawn from the United States market by the FDA after a study showed that this compound resulted in an increased risk, albeit small, of hemorrhagic stroke.

Absent a well-controlled clinical study comparing ephedrine alkaloids to PPA, it is not possible to answer the question of whether ephedrine alkaloids pose the same increased risk for hemorrhagic stroke as PPA. While the AMA supports well-controlled clinical studies on the relationship of serious adverse events to ephedrine alkaloids, these studies are not a necessary prerequisite to removing dietary supplement products containing ephedrine alkaloids from the market immediately.

*Question 3. Should herbal ephedra be available by prescription only in the United States?*

For reasons stated above, the AMA strongly supports the removal of dietary supplement products containing ephedrine alkaloids from the United States market. Whether products containing ephedrine alkaloids that are regulated as drugs should be available in the United States remains an open question. A product sponsor (manufacturer) would have to submit evidence of safety and efficacy for one or more indications to the FDA for premarket review. If the evidence shows a benefit/risk ratio that justifies approval for marketing, then such a product could be marketed. Whether the product is available OTC or only by prescription would depend on the product's safety and on the need or lack of need for physician supervision of patients using the product.

*Question 4. What are the dangers of taking ephedra-containing products without medical supervision?*

Because of ephedrine's known sympathomimetic effects on the cardiovascular and central nervous systems, reports of cardiac arrhythmias, myocardial infarctions, sudden death, strokes, and seizures are not unexpected. These types of severe adverse events have been reported in the medical literature for many years. If individuals have a known pre-existing condition (e.g., cardiovascular disease) that makes them more susceptible to these complications of ephedrine, then medical supervision could prevent the complication from occurring (e.g., by advising the patient not to use ephedrine). Ephedrine rarely is used today for medical purposes because many other drugs are more effective and have fewer adverse reactions. However, if a physician were to recommend ephedrine for medical purposes, the risks could be weighed against the benefits.

As discussed above, the real problem with dietary supplements containing ephedrine alkaloids is that there is no, or at best questionable, benefit in using the product. No medical condition or illness is prevented by having ephedrine in your diet. Yet ephedrine alkaloid-containing products do have risks and, in some cases, these risks may be serious or fatal to previously healthy young people who do not experience any benefit from the product. These serious side effects, regardless how rare they may be, are unacceptable in the absence of proven benefits, and the products should be removed from the market.

*Question 5. Please explain the difference between a patient taking a prescription drug for obesity under the supervision of a physician and a consumer taking an ephedra product for obesity without any screening for medical conditions that would suggest that the consumer was a poor candidate for such a product.*

Appropriate treatment of overweight and obese patients requires a comprehensive approach involving diet and nutrition, regular physical activity, and behavioral change, with an emphasis on long-term weight management rather than short-term extreme weight reduction. The aggressiveness of the treatment approach should be tailored to match the health risks associated with the patient's weight. Available treatment options vary in their effectiveness and risk. Physicians have an important role in promoting preventive measures and encouraging positive lifestyle behaviors, as well as identifying and treating obesity-related comorbidities. Physicians also fulfill a vital function in counseling patients about safe and effective weight loss and weight-maintenance programs, referring patients to ancillary personnel when appropriate, and providing monitoring, support and encouragement to the patient.

Prescription anti-obesity drugs should be given only as an adjunct to nutrition therapy and exercise. The AMA concurs with the following NIH recommendations for the pharmacologic treatment of adult obesity:

- lifestyle therapy (diet, exercise) should be considered before any drug therapy;
- weight-loss drugs approved by the FDA may be used as part of a comprehensive weight-loss program for patients with a body mass index (BMI) $\geq$ 30 kg/m$^2$ with no accompanying obesity-related risk factors or diseases (e.g., hypertension, dyslipidemia, coronary heart disease, type 2 diabetes, and sleep apnea), and for patients with a BMI $\geq$ 27 mg/m$^2$ with accompanying obesity-related risk factors or diseases;
- avoid use of drugs without accompanying lifestyle modification;
- assess drug efficacy and safety continually;
- discontinue drug use if it is ineffective in weight loss or weight maintenance, or if there are serious side effects. Pharmacotherapy cannot be expected to continue to be effective in weight loss or weight management after cessation of drug therapy.

To prevent weight regain, weight-loss drugs need to be used on a long-term basis in the same fashion as agents for other chronic disorders, such as hypertension, hyperlipidemia, and diabetes. In order to be used on a long-term basis, weight-loss medications must be both safe and effective. Because many obese patients have underlying cardiovascular and endocrine conditions, physicians should be involved to monitor for adverse effects, as well as drug efficacy.

Dietary supplements (e.g., ephedra alkaloids in combination with caffeine) that promise quick and easy weight loss without physician supervision are attractive to consumers. However, combining the stimulants caffeine and ephedra,

particularly without medical supervision, may increase the risk of adverse events. Additionally, poor quality control may contribute to the problems associated with the safety and efficacy of ephedra-containing dietary supplements. No two ephedra-containing supplements are the same. They contain multiple alkaloids of varying potency, and significant differences between label claims and actual contents of ephedra alkaloids have been noted, both among within specific products. The AMA continues to be concerned that the FDA has not, as of this date, released proposed regulations for Good Manufacturing Practices for dietary supplements.

As noted earlier, because of the unpredictable amounts of active ingredients and the potential for harmful side effects, the NIH guidelines for the treatment of obesity state that herbal preparations, including ephedra-containing products, are not recommended as part of a weight-loss program**.** Without medical supervision, some individuals who might be discouraged by previous failures to lose weight may combine medications, or use dietary supplements at doses higher than what is recommended.

*Question 6. Please discuss any initiatives that the AMA has taken to ensure that in discussing weight loss with their patients, physicians explain the possible dangers of ephedra-containing products.*

The AMA is currently developing a document entitled "Assessment and Management of Adult Obesity: A Primer for Physicians and Other Health Professionals." One component of this guide deals with pharmacologic management and will address the role of dietary supplements for weight loss. This document is expected to be released next year. When it is issued, the AMA would be pleased to share this primer with members of the Subcommittee.

Thank you for the opportunity to testify before the Subcommittee. The AMA looks forward to working with you to protect patients' health.