American Medical Association
Physicians dedicated to the health of America

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Food and Drug Administration
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Rockville, MD 20852

RE: Dietary Supplements Containing Ephedrine [Docket No. 95N-0304]

The American Medical Association (AMA) would like to commend the Commissioner of the Food and Drug Administration (FDA) for reopening the comment period regarding the health risks associated with dietary supplements containing ephedrine (or ephedra) alkaloids (Federal Register. 2003;68(43):10417-10420). As previously stated in letters to the FDA in September 2000 and in January 2002 and in testimony before Congress in October 2002, the AMA urges the FDA to initiate proceedings to remove dietary supplements containing ephedra alkaloids from the United States market.

Under the "Dietary Supplement Health and Education Act of 1994" (DSHEA), in order to remove a product from the market, the FDA must demonstrate that a dietary supplement presents an "unreasonable risk of illness or injury" to American consumers under conditions of use recommended or suggested in labeling. The AMA firmly believes that new scientific evidence that has come to light in recent months has made an even more convincing case that this "unreasonable risk of illness or injury" exists.

Dietary Supplements Should Be Regulated To the Full Extent Possible Under Current Law

Dietary supplements are classified as foods under DSHEA. Unlike drugs, rigorous safety and efficacy standards are not required for these products, and current good manufacturing practices (CGMP) regulations to assure the quality of dietary supplements were proposed only within the past month. While the benefit/risk ratio for drugs is based on rigorous scientific study and premarket regulatory review by the FDA, the benefit/risk ratio of dietary supplements is far less certain.

The AMA believes that DSHEA fails to provide for adequate 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.

Even in the absence of modifications to the current federal law, however, the FDA must aggressively regulate dietary supplements, including ephedra, 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, as discussed above, are subject to limited regulatory oversight. In other words, it is imperative that dietary supplement products have essentially no risks, i.e., they must be extremely safe, and provide some benefits for consumers. This is currently not the case for ephedra.

The Risks of Ephedra Alkaloids Far Outweigh Their Benefits

The AMA believes that dietary supplement products containing ephedra alkaloids fail to satisfy the requirement for a high benefit/risk ratio. In fact, after evaluating the totality of the available scientific evidence on the benefits and risks of dietary supplements containing ephedra alkaloids, the AMA argues that their risks *far* outweigh the benefits. The AMA has taken this position based on a number of considerations. Some of these considerations have been previously communicated to the FDA and others are based on new scientific evidence.

The FDA has received over 18,000 voluntarily submitted Adverse Event Reports (AERs) associated with dietary supplements containing ephedra. 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. Due to the nature of voluntary adverse event reporting systems, these AERs undoubtedly underestimate the actual number of adverse events that have occurred. For example, a 2001 report from the Office of the Inspector General of the Department of Health and Human Services (OEI-01-00-00180) concluded that current surveillance systems for identifying adverse reactions from dietary supplements probably detect less than 1% of adverse reactions.

A recent review of adverse reactions to ephedra and other herbal products reported to the American Association of Poison Control Centers' Toxic Event Surveillance System concluded that ephedra accounted for 64% of all adverse reaction reports for herbs, but ephedra-containing dietary supplements represented only 0.82% of herbal product sales. Based on these data, the authors concluded that the relative risk observed for ephedra-containing herbal products was more than 100-fold greater than for any other herb. The authors did not believe reporting bias could have accounted for this enormous difference in relative risk (see Bent et al. Ann Intern Med. 2003;138:468-471).

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 ephedra alkaloids could be identified for use in dietary supplements." It recommended that FDA remove dietary supplements containing ephedra alkaloids from

the market. Although the FDA did not implement the recommendation at that time, the AMA strongly urges it to do so as quickly as possible.

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 ephedra alkaloids in dietary supplements. Three of these experts believed that dietary supplements containing ephedra alkaloids posed a significant and unreasonable risk. One of these experts subsequently published his review of the 140 AERs and concluded that 31% of the cases were definitely or probably related to the use of supplements containing ephedra alkaloids. Among the definitely or probably related adverse events, three resulted in death and seven resulted in permanent disability (see Haller and Benowitz. N Engl J Med. 2000;343:1833-1838).

A recently published case-control study suggested that consumption of ephedra in dosages of greater than 32 mg per day results in a 3- to 4-fold increase in the risk of hemorrhagic stroke (see Morgenstern et al. Neurology. 2003;60:132-135). Although this study was limited by its statistical power, it signals a reason for concern about the use of ephedra in dosages above 32 mg per day. As discussed below, these higher doses of ephedra appear to be necessary to have an effect on weight loss. Furthermore, phenylpropanolamine, a sympathomimetic amine that is closely related to ephedrine and actually is a minor alkaloid in ephedra alkaloids, recently was removed as an over-the-counter drug in the United States because it increased the risk of hemorrhagic stroke in women (see Kernan et al. N Engl J Med. 2000;343:1826-1832).

The RAND Study: Recently, the results of the RAND study, commissioned by the National Institutes of Health (NIH) and the Agency for Healthcare Research and Quality, on the efficacy and safety of ephedra and ephedrine for weight loss and athletic performance were released to the public. Safety data from 50 clinical trials yielded estimates of 2.2- to 3.6-fold increases in the odds of psychiatric, autonomic, or gastrointestinal side effects, and heart palpitations. Moreover, upon review of over 18,000 case reports, the investigators identified 22 cases (2 deaths, 3 myocardial infarctions, 9 cerebrovascular accidents, 3 seizures, and 5 serious psychiatric events) as "sentinel events" and an additional 43 cases as "possible" sentinel events with prior (natural) ephedra consumption. Sentinel events were defined as adverse events that occurred within 24 hours of ephedra consumption and that excluded all other potential causes (see Shekelle et al. JAMA. 2003;289:1537-1545).

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 ephedra 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 ephedra alkaloids are of questionable benefit. Moreover, the AMA is unaware of any well-controlled clinical trials that prove efficacy for these purported uses. The AMA's view recently was supported by the RAND study, which concluded that there was insufficient data to support the use of ephedra for athletic performance (see Shekelle et al. JAMA. 2003;289:1537-1545). In fact, the FDA recently sent warning letters to manufacturers of ephedra-containing dietary supplements that are making unsubstantiated claims about sports performance enhancement. Taking into account the high number of actual or likely adverse events, the biological plausibility that many or most of these events were caused by the ephedra supplements, and the extremely questionable benefits of ephedra alkaloid-containing products, the AMA believes the benefit/risk ratio for these products is clearly unacceptable.

The RAND study, using meta-analysis, suggests that (synthetic) ephedrine and (natural) ephedra, the latter usually in combination with caffeine and other dietary supplement ingredients, promote modest short-term weight loss in clinical trials. However, the RAND study noted that there are no data regarding long-term weight loss (i.e., greater than six months) or on maintenance of weight loss after the products are discontinued. Furthermore, only six small clinical trials actually studied (natural) ephedra (the dietary supplement) and two of these trials were based on unpublished data. In all of these trials the daily dosage of ephedra exceeded 32 mg per day and the ephedra was combined with caffeine and other herbs. The pooled average percent weight loss in the ephedra-treated patients, compared with pretreatment weight, was only 5.2% at four months. As noted above, ephedra was associated with a 2.2- to 3.6-fold increase in the risk of psychiatric symptoms, autonomic symptoms, upper gastrointestinal symptoms, and heart palpitations in the clinical trials (see Shekelle et al. JAMA. 2003;289:1537-1545). The AMA strongly believes these very modest benefits of ephedra (combined with caffeine) on short-term weight loss are far outweighed by the side effects observed in clinical trials and, more importantly, by the serious risks that have been reported with the use of dietary supplements containing ephedra alkaloids. The AMA emphasizes that ephedra alkaloids are considered food supplements, rather than drugs, under current law. Because these products have limited regulation and are available to all Americans without a prescription or medical examination, dietary supplements containing ephedra alkaloids should be even safer than drugs and should have a much higher overall benefit/risk ratio when compared to drugs. Unfortunately, the available scientific evidence suggests that Americans who ingest ephedra products are being placed at significant risk.

Ephedra-Containing Dietary Supplements Should NOT be Used to Treat Obesity

Obesity is an extreme public health problem in the United States. 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. For these reasons, the AMA continues to take the position 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. The AMA concurs with the NIH guidelines for the pharmacologic treatment of adult obesity. The NIH guidelines state that herbal preparations, including ephedra-containing products, are not recommended as part of a weight-loss program (see http://www.nhlbi.nih.gov/guidelines/obesity/ob_gdlns.htm). It should be noted that in Denmark, ephedra alkaloids are available to treat obesity, but these products can be obtained only by prescription.

FDA Should Follow the Lead of Health Canada and Recall Ephedra-Containing Dietary Supplements from the United States Market

In 2002, 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.

The FDA should follow the lead of Health Canada and eliminate the health risks posed by these products for Americans.

"Unreasonable Risk" Should Be Determined Based on the Benefit/Risk Ratio

Under DSHEA, the burden of proof falls on the FDA if it wishes to take regulatory action against a dietary supplement. Specifically, the FDA must show that a supplement presents a "significant or unreasonable risk of illness or injury" under the conditions recommended or suggested in labeling (or under ordinary conditions of use if the labeling is silent). In its recent White Paper, *Evidence on the Safety and Effectiveness of Ephedra: Implications for Regulation*, the FDA raises the question regarding what level of evidence the Agency would need to conclude that a dietary supplement presents unreasonable risk. For example, should FDA be required to fund or conduct a rigorously controlled prospective clinical study to prove unequivocally that ephedra presents an unreasonable risk? Or, alternatively, can FDA make such a determination by using a benefit/risk calculus that examines the available scientific evidence and assesses whether ephedra's known or suspected risks outweigh its known or suspected benefits?

The AMA strongly argues that using a benefit/risk calculus should be sufficient for the FDA to determine if dietary supplements containing ephedra alkaloids present an "unreasonable risk." The AMA believes this is a fair and reasonable burden that the government must satisfy for a category of food products whose manufacturers have essentially no burden to demonstrate a positive benefit/risk ratio prior to marketing. On the other hand, if FDA is forced to fund or conduct an expensive and time-consuming prospective clinical study to prove unequivocally that ephedra (or any dietary supplement) is an unreasonable risk, it would be virtually impossible to remove unsafe dietary supplements from the market in a timely manner. This latter burden would be unreasonable and would seriously compromise the FDA's ability to protect the health of Americans from dietary supplements that present an unreasonable risk.

In the case of dietary supplements containing ephedra alkaloids, the benefit/risk ratio is very clear. Such products show marginal benefit for short-term weight loss, but have considerable side effects, and there are many adverse event reports linking these products to deaths or serious morbidity. Given that these products are classified as foods and are subject to virtually no regulation prior to marketing, American citizens have the right to expect that these products are extremely safe and have some benefits. This clearly is not the case for dietary supplements containing ephedra alkaloids.

Conclusion

In conclusion, the AMA urges the FDA to initiate proceedings to remove dietary supplements containing ephedra alkaloids from the United States market because the risks associated with the use of these products outweigh the benefits. These products, which are classified as food supplements, present an unreasonable risk to American consumers.

Sincerely,

Michael D. Maves, MD, MBA