American Academy of Orthopaedic Surgeons ® | AAOS American Association of Orthopaedic Surgeons ®

April 4, 2003

Mark B. McClellan, M.D., Ph.D.
Commissioner
Food and Drug Administration
5630 Fishers Lane
Rockville, Maryland 20852

Dear Dr. McClellan:

The American Academy of Orthopaedic Surgeons (AAOS/Academy), representing over 19,000 Board certified orthopaedic surgeons, welcomes the opportunity to comment on the Food and Drug Administration's (FDA) Dietary Supplements Containing Ephedrine Alkaloids Proposed Rule [Docket No. 95N-0304]. The AAOS realizes that the FDA is weighing several regulatory strategies concerning ephedra and products containing ephedrine alkaloids. As advocates for our patients, the AAOS recommends the highest standards for patient care and patient safety measures. The Academy will limit its comments to the following:

- The AAOS supports the removal of dietary supplements containing ephedrine alkaloids from the U.S. marketplace;
- The AAOS believes that a legislative solution may provide greater protection to the public than the Dietary Supplement Health and Education Act (DSHEA); and
- The AAOS recommends that the FDA redesign their adverse event data collection system.

THE AAOS SUPPORTS THE REMOVAL OF DIETARY SUPPLEMENTS CONTAINING EPHEDRINE ALKALOIDS FROM THE U.S. MARKETPLACE

Ephedra and products containing ephedrine alkaloids are currently regulated as dietary supplements under the DSHEA enacted in 1994. While medical products must prove safety and efficacy prior to marketing, the DSHEA places the burden of proof on the FDA to demonstrate that a dietary supplement or ingredient presents an unreasonable risk of illness or injury.

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Evidence from the 2003 RAND study, commissioned by the National Institutes of Health, compiled approximately 17,000 case reports of adverse events. Deaths, heart attacks, strokes, seizure, and psychiatric episodes are associated with the use of products containing ephedra and summarized in the RAND report. While case reports provide the lowest level of epidemiological evidence, the number and severity of adverse events from the meta-analysis in the RAND study in addition to other scientific literature, prove causality of serious events occurring with the use of ephedra products. Significantly, a recent article stated that products containing ephedra accounted for 64% of all adverse reactions to herbs in the United States while those products represented only 0.82% of the herbal market[1]. Similarly, Canadian data provided uncontrolled evidence that ephedra may increase the risk for hemorrhagic stroke[2]. Historically, the number of adverse events reported to health professionals and MedWatch is a minute fraction of the actual number of events occurring in the population.

The AAOS will analyze and submit comments on the "*Current Good Manufacturing Practice Manufacturing, Packing, or Holding of Dietary Ingredients and Dietary Supplements Proposed Rule*" and applauds the recent publication of the rule. However, the Academy is not aware of any studies that define a safe level of ephedrine alkaloid usage in dietary supplement products. The active alkaloid in ephedra, ephedrine, whether botanical or synthetic in nature, provides biological activity unlike the majority of dietary supplements. Of note, synthetic ephedrine is marketed in preparations for respiratory ailments and classified by the FDA as an over the counter drug. The Academy distinguishes ephedrine alkaloid products from the majority of dietary supplements as providing potential harm to the public. The AAOS believes that dietary supplements containing ephedra and ephedrine alkaloids present an unreasonable risk of illness or injury to the public and therefore should be removed from the U.S. marketplace.

THE AAOS BELIEVES THAT A LEGISLATIVE SOLUTION MAY PROVIDE GREATER PROTECTION TO THE PUBLIC THAN THE DIETARY SUPPLEMENT HEALTH AND EDUCATION ACT:

Since the DSHEA allows for the marketing of products without prior safety and efficacy studies, the public may be unduly jeopardized by some classes of dietary supplements. The Academy believes that this is the case with supplements

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[1] Bent, S, Tiedt, TN, Odden, MC, Shlipack, MG,. The Relative Safety of Ephedra Compared with Other Herbal Products. Ann. Intern. Med. 2003:138.

[2] Simon, JE, Morgan, SC, Pexman, JHW, et. al. The Use of Ephedra-Containing Products and Risk for Hemorrhagic Stroke. Neurology: 2003;60:132-135.

containing ephedrine alkaloids. The FDA has been alerted to problems with products containing ephedrine alkaloids for many years but has not been able to meet the legal challenge outlined in the DSHEA. While the RAND meta-analysis should provide sufficient data to meet the burden of proof, the Academy believes that many adverse events occurred unnecessarily.

The AAOS supports the development of new legislation that will classify dietary supplements according to a risk based regulatory scheme. While most vitamins and minerals are used by the American public without incident, the regulatory framework should be most stringent if a supplement produces a pharmacological effect.

A new regulatory framework should be developed to enable the FDA to remove products that pose a significant risk to the public. Under DSHEA, post-marketing surveillance has proven to be inadequate in protecting public health. A greater burden of proof must be placed on the manufacturers of dietary supplements prior to marketing their products.

The AAOS agrees with several recommendations outlined in the Office of Inspector General's report *"Adverse Event Reporting for Dietary Supplements: An Inadequate Safety Valve"* (April 2001 OEI-01-00-00180). The Academy supports collaboration with the National Institutes of Health in defining a research agenda to address safety issues, the development of a monograph system for dietary supplements that would contain safety information on selected ingredients, and collaboration with the United States of Pharmacopeia in providing standardization on many dietary supplement ingredients.

THE AAOS RECOMMENDS THAT THE FDA REDESIGN THEIR ADVERSE EVENT DATA COLLECTION SYSTEM

Presently, the FDA could enforce the general rule making authority under 701(A) of the Federal Food, Drug, and Cosmetic Act to demand that manufacturers report all adverse events to the FDA. The Academy supports this action thereby providing FDA with a more comprehensive database of adverse events. Nevertheless, the FDA is in need of significant improvements to their information technology systems to ensure useful data collection. The FDA must devote significant resources to design a system that is both user-friendly and interactive. A well-designed data collection system should provide an early warning system for problems with biologics, drugs, devices and dietary supplements.

Finally, the AAOS is supportive of patient safety efforts and has a long history of producing and implementing programs to provide education to the public. The safety of all patients is of paramount importance to the AAOS.

CONCLUSION

In summary, we urge the FDA to take appropriate actions to provide for the safety of the American public. The Academy believes that dietary supplements containing ephedrine alkaloids should not be available in the U.S. market due to an unreasonable risk of injury or illness. We share the concerns of the FDA in ensuring safe and effective products for all patients. The AAOS appreciates the FDA's willingness to seek perspectives on regulatory alternatives for ephedra products and to seek input from professional medical associations. The AAOS looks forward to working with the FDA on future efforts to increase patient safety.

Sincerely,

William W. Tipton M.D.

William W. Tipton, Jr., MD
Director of Medical Affairs