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COMMENT ON
"DIETARY SUPPLEMENTS CONTAINING EPHEDRINE ALKALOIDS"

by

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Ephedra is a naturally occurring substance derived from the Chinese herb Ma Huang. For purposes of this Comment, ephedra refers to a group of botanical preparations used for weight loss and to enhance athletic performance. It is an adrenaline-like stimulant with potentially powerful effects on the human cardiovascular and nervous systems.[1] Its principle active ingredient is ephedrine, one of six naturally occurring ephedrine alkaloids (EADS) in ephedra. Ephedrine exerts its effect on the cardiovascular system (increased heart rate and increased blood pressure) and on the central nervous system (psychoactive effect characterized by an alleged sense of well being) ten times longer than epinephrine.[2] Whereas epinephrine is regulated by the FDA, the longer-acting stimulant ephedrine, in its natural state, is not. However, chemically-synthesized ephedrine is subject to FDA regulation. When classified as a drug, ephedrine is not approved for long-term use.[3]

The FDA regulates ephedra under the Dietary Supplement Health and Education Act (DSHEA) of 1994. The FDA has the burden of showing that the risk of illness from use of this product is significant or unreasonable before it is authorized to exercise regulatory action. This burden entails a risk/benefit analysis that weighs and balances the safety concerns associated with ephedra use against the potential benefits from ephedra's use.

At this time, there is little evidence suggesting that ephedra is effective for weight loss, unless used in conjunction with strategies that are effective without ephedra. High-quality, randomized, controlled, clinical trials are needed to determine whether EADS are safe and effective for weight loss or body-building, especially for long-term use of ephedra. Unfortunately, the

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[1] FDA News, HHS Acts to Reduce Potential Risks of Dietary Supplements Containing Ephedra,2/28/03

[2] Jones, WK. Report of Public Meeting: "Safety of Dietary Supplements Containing Ephedrine Alkaloids", August 8-9, 2000, Washington, D.C. (available at http://cfscan.fda.gov/~dms/ds-ephe3.html)

[3] FDA White Paper on ephedra, Evidence on the Safety and Effectiveness of Ephedra: Implications for Regulation (available at http://www.fda.gov/bbs/topics/NEWS/ephedra/whitepaper.html

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manufacturers have no incentive to evaluate ephedra's safety since they are already selling it, and they have even less incentive to reveal any safety concerns they may have.

Controlled trials, conducted and prepared for the Agency for Healthcare Research and Quality, concluded that the use of ephedrine or ephedra-containing dietary supplements or ephedrine plus caffeine were associated with two or three times the risk of nausea, vomiting, autonomic hyperactivity, palpitations, and psychiatric symptoms such as anxiety and change in mood.[4]

Surgeons and anesthesiologists are cautioned to conduct thorough pre-screening histories on their surgical patients with specific and targeted questions regarding the patient's recent use of ephedra. Hospital researchers concluded that adverse events such as increased bleeding tendencies and drug interactions were associated with the use of ephedra.[5] An article published in the *Journal of the American Medical Association* recently reported that ephedra "may pose a concern during the perioperative period. Complications can arise from these herbs direct and pharmacodynamic or pharmacokinetic effects. Direct effects include...cardiovascular instability from ephedra." [6]

In addition to the research findings, there are more than 1,000 documented voluntary adverse event reports relating to the use of herbal ephedra.[7] These adverse events include hypertension, arrhythmias, tachycardia, nervousness, headache, dizziness, palpitations, skin flushing, tingling, and insomnia.[8] Between January 1993 and February 2001, the FDA's Special Nutritional Adverse Event Monitoring System documented 137 deaths associated with EADS; 38 myocardial infarctions associated with EADS; 98 reports of cardiac arrhythmias associated with EADS; 85 cerebrovascular accidents associated with EADS, and 121 seizures associated with EADS.[9]

Unfortunately, published studies have not adequately addressed the long-term risks of ephedra, either alone or in combination with the stress of exercise or the use of other stimulants such as caffeine.

The Department of Health and Human Services has the authority to remove or ban a product if it poses an imminent hazard to the public health and safety. The research and adverse events described above clearly indicate the serious and immediate public health hazards associated with the use of ephedra.

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[4] Shekelle, PG, ML Hardy et al. "Ephedra and ephedrine for Weight Loss and Athletic Performance Enhancement: Clinical Efficacy and Side Effects", Agency for Healthcare Research and Quality, February 2003 (available at http://www.fda.gov/bbs/topics/NEWS/ephedra/summary.html)

[5] Hodges, PJ and PC Kam. "The Perioperative Implications of Herbal Medicines", Anesthesia, 57 (9):889-99, September 2002.

[6] Ang-Lee, MK and J. Moss et al. "Herbal Medicines and Perioperative Care", JAMA, 286(2):208-16, July 11, 2001.

[7] Shekelle, Supra

[8] Jones, WK, Public Meeting: Safety of Dietary Supplements Containing Ephedrine Alkaloids, August 8-9, 2000

[9] Public Citizen Letter to AMA urging support of HRG petition to ;the FDA to ban dietary supplements containing ephedrine alkaloids, January 17, 2002

We agree with the American Medical Association's recent testimony before the U.S. Senate, which states "AMA urges FDA to remove dietary supplements containing ephedra from the market... The risk/benefit ratio for these products is unacceptable."[10] The AMA pointed out that "because of ephedra's effects on the cardiovascular and central nervous systems, it may cause cardiac arrhythmias, heart attacks, strokes, seizures and sudden death in both previously healthy people, as well as in those with risk factors for these conditions." We believe that Health Canada made an appropriate decision when they issued an Advisory not to use products containing ephedra or ephedrine, either alone or in combination with caffeine and other stimulants.[11]

Since the use of ephedra has increased dramatically in recent years, the FDA should immediately take action to protect the public from the risks posed by this widespread use. Unless research is done that clearly proves that ephedra is safe and effective for certain populations, it should be removed from the market in the United States.

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[10] http://www.ama-assn.org/ama/pub/article/1616-6825.html

[11] http://www.hc-sc.gc.ca/english/protection/warnings/2001/2001_67e.htm