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The Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

RE: Comments on the 1997 proposed rule pertaining to dietary supplements containing Ephedra and the Dietary Supplement Health and Education Act (DSHEA) (Docket No. 95N-0304)

To whom it may concern:

The American Society for Clinical Pharmacology and Therapeutics (ASCPT) wishes to add its support and make specific comments with regard to initiatives within Food and Drug Administration (FDA) to critically evaluate Ephedra (and ephedrine) as a constituent in both over-the-counter drugs and dietary supplements. A previous opinion on this issue from ASCPT was sent to Dr. Bernard A. Schwetz on 06 March 2002.

By way of introduction, ASCPT represents the largest professional organization in the world devoted to the discipline of human clinical pharmacology. Our society is comprised of 2000 scientists from the U.S. and abroad with representation from the disciplines of medicine, pharmacy, dentistry and nursing. The general mission of ASCPT is to promote the development and safe use of medications in humans through application of the broad principles of clinical pharmacology. The potential risks to public health associated with the un-regulated, wide availability and use of dietary supplements and/or complimentary-alternative medications containing Ephedra in any form provides just cause for ASCPT to offer comment.

Our previous letter to Dr. Schwetz articulated the opinion of ASCPT that the "current, wide unregulated use (of Ephedra) in the United States appears to pose a serious health risk to adults, both young and old." Evidence cited in support of this opinion included a peer-reviewed publication describing an apparent clear association between Ephedra and serious cardiovascular and central nervous system toxicity leading to death and disability (*N Engl J Med* 2000;343:1833-1888) and actions by Health Canada which, on 09 January 2002, announced a voluntary recall of a wide range of drug products containing Ephedra or ephedrine, claiming that large amounts "pose a serious risk to health." Based on this information, ASCPT recommended that the Agency "take clear and decisive action" to protect public health by using the imprimatur afforded to the Food and Drug Administration by Congress through charter and mandate.

The opinion of ASCPT on this issue has been reinforced over the past 12 months and hence, we reiterate our position that prompt and definitive action by FDA to regulate and potentially remove Ephedra-containing products from the U.S. market remains in order.

95N-0304

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1. The potential dangers of Ephedra

Recent reports continue to support the widely held association between Ephedra and both morbidity and mortality. Since our initial letter of March 2002, numerous reports on the potential adverse health risks associated with Ephedra and its alkaloids have been published in the peer-reviewed medical literature. While ASCPT can not and will not endorse nor comment upon the quality and/or validity of the information contained in these published reports, we do note that they range in scope from *in vitro* findings associated with inhibition of normal growth/differentiation in human endothelial cells (*Phytother Res* 2003;17(2): 107-111) to reports of associated mania (*Pharmacotherapy* 2003;23(3): 380-383), sudden hearing loss (*Am J Health Syst Pharm* 2003;60(4): 375-377), increased risk of hemorrhagic stroke (*Neurology* 2003; 60: 132-135), analyses of adverse event reports associated with ephedra (*Mayo Clinic Proc* 2002; 77: 12-16, *Clin Pharmacol Ther* 2002; 71; 421-432), and heatstroke associated with cardiovascular collapse and death (*Br Med J* 2003;326: 464). Also, results from a comparative case series study reported that the relative risk for adverse reactions from Ephedra were considerably greater than those from kava, Ginkgo biloba, or all "supplements" combined (*Ann Intern Med* 2003;138(6): 468-471).

2. The appropriateness of warning labels as a means for insuring public safety

The assumed utility of warning labels to prevent an adverse drug reaction is, to a great degree, derived through inference as opposed to being demonstrated from carefully conducted phase IV clinical trials. This may be further compounded for a substance not viewed by the consumer as a "medication" but rather, a dietary supplement as is the case for the majority of products containing Ephedra. As well, warning labels would be of no utility to individuals with unrecognized medical conditions (eg., hypertension, hyperthyroidism, vascular malformations of the brain, subclinical cardiac arrhythmias) that might predispose them to adverse reactions produced by Ephedra.

Warning labels are appropriate only when efficacy for intended use has been demonstrated by adequately designed and controlled clinical trials, and the risk-to-benefit ratio indicates an adequate safety margin in the target population. To date, only highly selected, small populations have been used in short-term studies of Ephedra-induced weight loss (*Int J Obes* 2001; 25: 316-324, *Int J Obes* 2002; 26: 593-604, J Am Med Assoc 2003; 289: 1537-1545). These trials have reported marginal efficacy and increased frequency of drug-related dropouts or side effects, and have been criticized for the absence of long term follow-up and assessment of a rebound effect (*J Am Med Assoc* 2003; 289: 1537-1545). No large scale clinical trials in an obese population have been reported, so there is inadequate assurance of safety for this indication. In addition, a review of the studies of ephedra-enhanced athletic performance regarded the evidence as inconclusive, yet found sufficient evidence to identify a 2 to 3 fold increased risk of side effects (*J Am Med Assoc* 2003; 289: 1537-1545). In light of the current state of knowledge, there is marginal or inadequate evidence of efficacy and clear risk of harm with ephedra. Therefore, ASCPT believes that the proposed warning labels are insufficient to address the adverse reactions of Ephedra in the absence of clear evidence of efficacy.

3. Maintaining the availability of Ephedra products to the public in the absence of evidence supporting their clinical utility as a medication

A significant or unreasonable risk of illness or injury associated with the ingestion of any dietary "supplement" or drug is likely to result when there is an absence of information that: a) substantiates a clear therapeutic benefit; b) describes a predictable relationship between exposure (dose) and response (both desired and

adverse) and c) when the proper dose (for age, illness or with concomitant medications with potential for interaction) is either not known or achievable from a given formulation/product. This is the case for products containing Ephedra in any form. Information on Ephedra available to the all of the licensed health care practitioners through recognized therapeutic compendia clearly support that this substance is a drug and hence, any decision to use it should be driven by the fundamental principles of pharmacology and therapeutics with oversight by medical practitioners capable of monitoring treatment and continually evaluating the risk vs. benefit profile of the drug. This is not the current practice being used for products containing Ephedra. In contrast, its use is driven by decisions emanating from practices of "self-medication" or alternatively, upon recommendation from non-medical practitioners who do not possess sufficient knowledge to appreciate the risks of treatment and/or truly view these products as dietary supplements despite their having no known value in human nutrition.

4. ***Implications of changing current law to enable FDA to more effectively address potential adverse health risks associated with Ephedra***

Simply stated, DSHEA was intended to address dietary supplements; compounds claimed to provide nutritional value for humans. This is not the case for products containing Ephedra where a pharmaceutical agent used by the lay public to facilitate weight loss, enhance athletic performance, and/or increase mental alertness is disguised as a safe supplement or adjunct to human nutrition. Existing FDA regulations for the development, approval and marketing of drug products would be more than sufficient for addressing potential adverse health risks associated with products containing Ephedra or any other agent that is accurately classified as a drug. It is the opinion of the ASCPT that the DSHEA should be modified to authorize FDA oversight of dietary "supplements" regarding their safety and health claims. Furthermore, reporting of adverse events by manufacturers should be required, and the FDA empowered to require evidence of safety when anecdotal adverse event reports are sufficient to raise concerns related to safety.

5. Availability of clinical research demonstrating the dangers of Ephedra-containing products

Considerable information exists concerning the clinical pharmacology of ephedrine, its potential adverse event profile and its therapeutic use. This information was reviewed by an FDA Advisory Committee in 1996 which concluded that "there is no safe dose of ephedra when taken without medical supervision". To conduct additional controlled clinical trials of products containing Ephedra where the content of active ingredient or potency based upon the original source of the drug (or its processing) is not known would be virtually impossible based upon existing FDA regulations which govern drug development and approval. As well, a an institutional review board (IRB) would likely not approve such a clinical trial in the absence of information to suggest that either direct or generalizable benefit from a clinical trial would outweigh the potential adverse health risks. Thus, evidence to support further controlled investigation of Ephedra as a drug or nutritional supplement is not apparent based on existing information and the availability of drug products (both prescription and over-the-counter) with well characterized clinical pharmacology and safety profiles.

In closing, it remains the opinion of ASCPT that products containing Ephedra offer the public only the potential for harm and no potential therapeutic benefit. Accordingly, the only mechanism that will protect the public is to remove these products from the market. Further, ACSPT recommends that FDA consider all

dietary "supplements" which are recommended for the treatment of a medical condition be regulated as drugs with the requisite standards of product quality and evidence of efficacy and safety.

Thank you for your consideration of this recommendation. If you have questions regarding the position of ASCPT on this issue or need additional information, please contact our Executive Director, Ms. Sharon Swan, at (703) 836-6981.

Sincerely,

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President

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President Elect