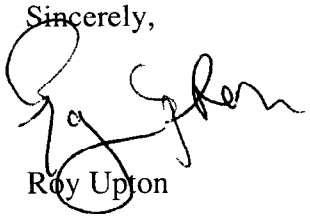
2188 '03 APR 25 A9:20

April 21, 2003

Dear Friends,

We submitted comments regarding ephedra. There were a few typos that left the meaning of a few sentences unclear. Enclosed are copies of the corrected versions. I understand that it is past the submission date but these new copies should make your review easier.

Sincerely,



Roy Upton

95N-0304

C4006

Docket No. 095N--0304

BEFORE

THE UNITED STATES OF AMERICA

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

ON THE PROPOSED RULE FOR

DIETARY SUPPLEMENTS CONTAINING EPHEDRA ALKALOIDS

UPON THE REOPENING OF THE COMMENT PERIOD

Submission by

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April 7, 2003

Preamble

The companies submitting these comments all specialize in the traditional use of herbal supplements including those that, presently or in the past, contain ephedra (*Ephedra sinica*). Due to changes in insurance coverage regarding these products, primarily due to concerns raised about ephedra use by FDA and the media, numerous companies have chosen to discontinue trade of this botanical. This will severely curtail the availability of this herb for its proper use. Some of the submitting companies exclusively distribute products directly to health professionals rather than in retail markets and maintain technical personnel that are highly trained in traditional Chinese and western herbalism and want to insure that the integrity of traditional herbalism is maintained. Each company is a member in good standing of the American Herbal Products Association (AHPA). However, the comments presented are those of the companies themselves and not of AHPA who has submitted their own comments. The concerns expressed jointly by these companies are of particular importance to this community and will support most of AHPA's positions, elaborate on issues of particular concern, and expand on some areas not fully addressed by the comments of others.

Summary of Key Points (elaboration on these points follows)

1) Based on the available data, dietary supplements containing ephedra or ephedrine alkaloids within the proscribed limits of traditional and OTC use and the trade recommendations of the American Herbal Products Association (AHPA) DO NOT PRESENT AN UNREASONABLE HEALTH RISK WHEN USED APPROPRIATELY ACCORDING TO LABELING DIRECTIONS.

2) Clear distinctions must be made between the various types of ephedra-derived products namely: crude ephedra herb and products made from crude ephedra herb; concentrated sources of ephedra alkaloids (predominantly ephedrine); products containing ephedra/ephedrine and other stimulants such as caffeine; and OTC drugs.

3) OTC dosages and indications for ephedrine and pseudoephedrine products are appropriate.

4) For ephedra dietary supplements, a claim of support as "traditionally used to support respiratory health" is appropriate.

5) Qualified health professionals utilize ephedra for other conditions as well as respiratory health, according to the tenets of their traditional system. Such uses must not be prohibited.

6) The propensity of reporting of adverse effects for the various classes of products is not the same. Therefore, each class must be addressed individually to insure appropriate health professional/consumer access while ensuring public safety. Serious adverse events associated with the appropriate use of ephedra have been rare. Most reports of alleged adverse effects have been associated with ephedrine alkaloid products and ephedra/ephedrine-caffeine products. This does not necessarily mean the

two classes of products vary in their safety profile but rather may be reflective of the differing demographics of the consuming populations.

7) The consuming population of athletic performance and weight loss products may be at higher risk of developing adverse effects such as those reported due to this population's inherent increased potential of high blood pressure (obesity) and stress (athletic performance), both of which can be exacerbated by sympathomimetic agents.

8) Traditional ephedra products yield a lower or similar concentration of ephedrine alkaloids as OTC ephedrine products. Therefore, ephedra dietary supplements should be subject to similar dosage restrictions and labeling requirements as those for OTC drugs. To require more restrictive labeling on ephedra dietary supplements and not require the same restrictions on ephedrine OTC drugs may constitute an unfair application of the law. If ephedrine is safe in the dosages and the parameters established for OTC drugs then it is safe within the same parameters as dietary supplements.

9) There are little data to support the use of ephedra for enhanced athletic performance. We do not believe this to be an appropriate indication for ephedra dietary supplements and believe that such claims should be prohibited from use on ephedra-containing dietary supplements.

10) If ephedra-caffeine products are shown to be effective for weight loss these should be subjected to a review within the OTC drug category with appropriate restrictions. In our opinion, combinations of ephedra and caffeine for weight loss are not appropriate within the regulatory class of "dietary supplements".

11) Qualified health professionals, namely licensed, certified, and or registered acupuncturists, naturopathic physicians, and herbalists should maintain access to ephedra for its traditional use. Modified labeling requirements should be developed for health professionals who are compounding directly for patients in which standard packaging is not available and for products marketed directly to health professionals and are not available in a retail setting.

12) The root of ephedra is also used and has not been implicated in any adverse events and thus should be treated as a completely separate entity with no labeling or access restrictions imposed.

13) FDA has the authority to impose restrictions on the sale and marketing of dietary supplements when it has been shown that such restrictions are justified.

14) Future initiatives should include the development of a formal safety and efficacy review panel similar to the Commission E of Germany and the development of a traditional medicines category of therapeutic goods for botanicals as is done throughout the world.

Basic Assessment of Safety

Based on the available data, dietary supplements containing ephedra or ephedrine alkaloids within the proscribed limits of traditional and OTC use and the trade recommendations of the American Herbal Products Association (AHPA) DO NOT PRESENT AN UNREASONABLE HEALTH RISK WHEN USED APPROPRIATELY ACCORDING TO LABELING DIRECTIONS. This opinion is firmly supported by generations of use of traditional preparations and decades of safe use of ephedrine-containing OTC drugs.

Distinguishing Between Traditional and Modern Products

Ephedra has been used in Chinese herbalism at least since the 1st century AD where its use was first ascribed as originating with the *Shen Nung Ben Cao Jing*. Since that time it has held a primary role in Chinese herbalism, forming the basis of numerous traditional Chinese herbal formulas, some that have been in continued use for almost two thousand years (Han dynasty).

In the 1780s, scientists discovered the alkaloid ephedrine and ascribed much of the pharmacological use of ephedra to this compound. Its pharmacology as a sympathomimetic is well known and does not need to be described here. The eventual synthesis of the alkaloids contained therein formed the basis of a number of over the counter (OTC) drugs that have remained on the market, with relatively few reports of serious adverse effects, for decades.

In traditional herbal use, ephedra is rarely used alone, but rather is combined with other botanicals, many of which, according to traditional principles of compounding, are considered to mollify the inherent stimulant actions associated with ephedra (Sionneau 1997). Moreover, according to traditional principles of herbalism ephedra is clearly indicated for certain conditions and health needs, most of which are similar to approved OTC indications for ephedra/pseudoephedrine products, and contraindicated in other specific situations, such as in hypertension, tachycardia, excessive sweating, and nervous tension (Bensky and Gamble 1993).

In addition to its use with other botanicals as well as its specific indications, traditional ephedra products generally yield much lower amounts of total alkaloids (than do OTC drugs) and are characterized completely differently than the weight loss and athletic products that have been subject to adverse reports (see addendum A). In traditional herbalism, they are not combined with stimulants such as caffeine and they are not marketed or intended for weight loss and athletic performance.

Recommendation: This coalition feels that appropriate regulatory guidelines have to be applied to the various classes of ephedra/ephedrine products and that the unique nature of each have to be considered. Specifically, 1. The warning label established for OTC ephedrine-containing drugs is appropriate for ephedra-containing dietary supplements whose ephedrine alkaloid yields are within the proscribed limits of traditional formulations and the OTC monograph (no more than 150 mg of ephedrine daily) and are

intended for use to support respiratory health; 2. Claims for enhanced athletic performance is not an appropriate claim for ephedra/ephedrine-containing supplements and should be prohibited; 3. If the available evidence supports the use of ephedra/ephedrine-caffeine products for weight loss, these products for this indication should be subject to review for approval as OTC drugs. We do not believe weight loss to be an appropriate claim for ephedra/ephedrine-caffeine products.

Distinguishing Between the Safety Profile of Various Ephedra Products

The overwhelming majority of serious adverse events reported for ephedra/ephedrine products have been associated with weight loss and athletic performance products not traditionally used preparations. The validity of these reports have been subject to broad criticism (General Accounting Office) and the Agency's sponsored Rand Report has clearly articulated that case reports can not be used to determine causality in stating;

> " The majority of case reports are insufficiently documented to make an informed judgment about a relationship between the use of ephedrine or ephedra-containing dietary supplements and the adverse event in question."

Moreover, the available clinical trials of ephedrine-caffeine products reveal no such adverse events when the combination is used within its recommended dosage range. Therefore, while we recognize the potential for adverse effects to be associated with the misuse and abuse of ephedra products, we similarly question the veracity of the evidence used by FDA to initiate this action.

Regardless, the ability to review the reports of adverse effects associated with ephedra/ephedrine-caffeine related products is beyond the scope of this document. However, we believe it must be recognized and publicly acknowledged that the consuming population of athletic performance and, most especially, weight loss products are a relatively high risk population that are potentially more susceptible to adverse effects such as ephedra/ephedrine-caffeine products may produce. A similar opinion of the demographics of this population was shared by FDA in 1997 when it was first suggested that ephedrine-containing OTC drugs be removed from the market or subjected to the same labeling requirements as ephedra-containing dietary supplements. At the same time, FDA expressed concern about adverse effects associated with ephedrine-containing OTC drugs but determined this was due to intentional abuse with the finding that no increase in restrictions placed on this class of products was warranted.

Recommendation: Athletic performance and weight loss categories of products are often consumed by a population that is at a higher than normal risk for the types of side effects that can be associated with ephedrine-caffeine containing products. Sympathomimetics such as ephedra/ephedrine can increase blood pressure and initiate stress responses that can include tremors, palpitations, insomnia, tachycardia, and anxiety. Those who are obese have a higher incidence of hypertension and other conditions that may be exacerbated by use of ephedra. Other such symptoms may be apparent if the consumer is on a severely restricted diet. Athletes, especially body builders and competitive athletes

similarly may be prone to stress and hypertension that can give rise to an increased risk of adverse effects.

Therefore, for this reason, and other reasons to be discussed, we believe that ephedra and ephedrine-caffeine products should not be allowed to be marketed for weight loss and enhanced athletic performance as dietary supplements. If these products are continued to be allowed, the labeling and restrictions as proposed in 1997 in the citizen's petition of the AHPA should be adopted as mandatory on all such products. All other ephedra containing products sold as dietary supplements yielding similar or lower amounts of ephedrine alkaloids as OTC drugs and not containing stimulants such as caffeine should be subject to the same warning label as is required on OTC drugs. We believe the available evidence supports this recommendation and that FDA has the authority to impose such restrictions.

Dosage Recommendations

Traditional herbal products containing ephedra singularly or in combination with other botanicals as outlined in the standard literature (see Addendum A) yield lower or similar concentrations of total ephedrine alkaloids* on a per serving and daily basis than ephedrine-containing OTC drugs; < 25 mg per serving; < 150 mg of ephedrine in a 24 hour period, unless otherwise specified by a qualified health care provider. As evidenced by the lack of reports for both traditional and OTC products as well as the parameters of FDA's OTC ephedrine monograph, this dosage has been established to be safe, and provides a clear guideline for establishing dosage limitations on ephedra-containing dietary supplements. Such a proposal is relatively consistent with the citizen's petition of AHPA of 1997. We believe the Agency has the responsibility to acknowledge this citizen's petition and provide an explanation as to why these recommendations were not previously adopted. We believe the available evidence supports this recommendation and that FDA has the authority to impose such restrictions.

* Dose to be calculated on a 1% total alkaloids yield in ephedra of which an average of 70% constitutes ephedrine; typically no more than 21 mg ephedrine in a single serving and no more than 63 mg ephedrine daily

Appropriate and Prohibited Indications

Respiratory effects: The most appropriate use of ephedra and ephedra containing supplements is for its anticatarrhal, decongestant, and bronchodilating effects. As an OTC medication, these are the most recognized uses of these products. As dietary supplements, a structure and function claim of the use of ephedra to help support respiratory health is appropriate and should be allowed.

Recommendations: Continued access to ephedra for its proper use both as a medicine and as dietary supplements should be allowed with appropriate restrictions on the types of claims allowed for each product category as well as appropriate warning labels that are consistent with those required for OTC ephedrine drugs. We believe FDA has the authority to impose such restrictions.

Enhanced Athletic Performance: According to the Rand Report, there are little data supporting the safety and efficacy of ephedra or ephedrine-containing products for enhancing athletic performance. Moreover, the Chinese medical community and professional herbalists consider this to be an inappropriate indication for ephedra. Sympathomimetics initiate a flight or fight stress response that can increase heart rate and blood pressure, both of which can already be raised by those undergoing intensive exercise, thereby increasing the potential risk for coronary and cerebrovascular problems.

Recommendation: We believe that increased athletic performance is an inappropriate indication for ephedra and ephedrine-caffeine products and that dietary supplements of ephedra should be strictly prohibited from making such claims. We believe the available evidence supports this recommendation and that FDA has the authority to impose such restrictions.

Weight Loss: There is evidence, including from the Rand Report, to suggest that ephedra/ephedrine-caffeine products are equally as effective in promoting moderate reductions in weight as approved OTC drugs for weight management (Boozer et al. 2001; Shekelle et al. 2003; Yanovski and Yanovski 2002). However, we do not believe this indication or the combining of ephedra, ephedrine alkaloids and other stimulants such as caffeine is appropriate for dietary supplements. If the evidence bears out the efficacy of ephedrine-caffeine products for weight loss, we believe they should be subjected to the same level of review as conventional OTC medications with restrictions as deemed appropriate based on the review.

The dietary supplement category was specifically developed as a class of goods with recognized benefits in promoting health and preventing disease in relatively healthy individuals. We recognize that health benefits can be achieved through moderate reductions in weight in the overweight population, and that this can be achieved through the use of ephedra/ephedrine-caffeine supplements. However, we do not believe that pushing the body into a state of stress, such as occurs with the use of sympathomimetic agents, is a healthy approach to weight management.

Recommendations: We believe that the combining of ephedra with caffeine or other similar stimulants for weight loss should be prohibited as dietary supplements and that such products should be subjected to a review as OTC drugs if the evidence supports this indication. We believe the available evidence supports this recommendation and that FDA has the authority to impose such restrictions.

Availability, Access and Labeling to Health Professionals

Numerous companies market directly and exclusively to qualified health professionals, namely licensed, certified, and registered acupuncturists, herbalists and naturopathic physicians. This category of products is provided directly to patients who are then monitored or are consulted with in follow-up visits. Similarly, many herb practitioners compound directly for patients and do not have manufacturing facilities that allow for inclusion of the standard warning label. Modified labeling requirements should be developed for health professionals who are compounding directly for patients in which

standard packaging is not available and for products marketed directly to health professionals and not available in a retail setting. According to the experience of health professionals, and the seemingly lack of reports of adverse events due to practitioner recommended traditional ephedra products, it appears clear that such products do not constitute a public health risk.

Recommendation: The warning language used for OTC ephedrine-containing drugs should be used for products that will be directly sold to and through health professionals. For products dispensed as part of a bulk decoction formula that lack standard labeling, such as are compounded in Chinese herbal medicine pharmacies or by qualified health professionals, alternate means of disseminating the appropriate warning information should be allowed. This can be done through warning stickers on the dispensing package:

> "Warning: This formula contains ephedra (*Ephedra sinica*). Use only as directed by your health care provider. Do not use this product if you have heart disease, high blood pressure, thyroid disease, diabetes, or difficulty in urination due to enlargement of the prostate gland unless directed by your health care provider. Do not use if you have ever been hospitalized for asthma or if you are taking any prescription drug for asthma unless directed by your health care provider. Do not use if you are now taking a prescription monoamine oxidase inhibitor (MAOI) (certain drugs for depression, psychiatric, or emotional conditions, or Parkinson's disease), or for 2 weeks after stopping the MAOI drug. If you do not know if your prescription drug contains an MAOI, ask your health care provider or pharmacist before taking this product. Side effects of this product may include: nervousness, tremor, sleeplessness, nausea, and loss of appetite. If these symptoms persist or become worse, consult your health care provider." (Ephedrine OTC Monograph).

We also believe that the OTC label warning for ephedrine OTC drugs should be firmly established for traditionally used ephedra products as described and this regulation should have pre-emptive authority over individual state initiatives to develop alternate labeling. Uniformity in labeling will prevent confusion in the marketplace and minimize costs to industry.

Continued Access to Ephedra Root

In Chinese herbalism, the root of ephedra is also used (ma huang gen) and is considered to have effects that are opposite of ephedra stems (Chang and But 1987). To date, there have been no reports of adverse effects associated with the use of ephedra root. Therefore, none of these recommendations regarding labeling or restriction of the trade of ephedra herb should be required for ephedra root. These are two distinctly different products and must be treated as such.

FDA's Request for Comments Regarding Their Regulatory Authority

There is a misperception, apparently even among those within the FDA, that DSHEA reduced the Agency's regulatory authority over dietary supplements. While we

acknowledge that various aspects of FDA's authority were clarified and/or modified with DSHEA, it is our opinion that no regulatory authority was repealed. Specifically with regards to the ability to impose restrictive guidelines regarding the commerce of dietary supplements it appears evident that FDA maintains and has exercised this authority under sections 201(n), 403(a)(1), and 701(a) of the Foods, Drugs and Cosmetics act as long as the Agency's decisions are not judged to be arbitrary and capricious (section 706).

Future Initiatives

We believe that the dietary supplement category of foods offers a unique class of health promoting substances to consumers. As has been pointed out in the legislative history of DSHEA and in literally thousands of clinical studies, dietary supplements have the potential to reduce the risk of numerous disease conditions while also promoting a higher level of health. This category of Dietary Supplements should be preserved completely. However, only having the dietary supplement category does not address the full potential of the use of botanicals as medicines. The only current regulatory mechanisms for the approval of "medicines" is inappropriate for the majority of botanicals that have been part of the public domain for centuries. Rather, we believe that the US must look to the "Traditional Medicines" models that are so prevalent in the international community. This model is specifically designed to safeguard public safety, determine the relative efficacy of botanicals for limited indications, and foster a high degree of confidence in botanical products. Such models exist throughout Europe, Canada, and Asia. The European Union is currently working on developing a harmonized system for all member nations. The development of such a model requires a review of international models as well as the cooperation of academicians, herbal practitioners, industry representatives, and regulators—not only regulators.

Similarly, the US would do well to establish a formal commission similar to the Commission E of Germany in order to address issues such as that raised for ephedra. Such a Commission could be convened to review the available safety and efficacy data for the most common botanical products traded in the US and create a database of appropriate claims for self-limited conditions, adequate label recommendations regarding warnings, and proper dosages. Such findings could then be used by consumers, regulators, health professionals, and the industry in producing, reviewing, or choosing botanical products that have a relatively high degree of safety and efficacy. These two initiatives could bring a rational approach to the botanical medicine arena and would be of long-term benefit to the public. Like the development of the Traditional Medicines category, such a commission would have to be made up of regulators, medical practitioners, traditional herbal practitioners, academicians and industry representatives.

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