April 7, 2003

Via Electronic Submission and Federal Express 1890 '03 APR -8 A9:13

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

Re: Docket 95N-0304
Dietary Supplements Containing Ephedrine Alkaloids[1]

Dear Sir/Madam:

Nutraceutical Corporation (Nutraceutical) submits these comments on the Food and Drug Administration's (FDA's) proposed rule on dietary supplements containing ephedrine alkaloids (hereinafter "ephedra supplements").[2]

FDA's proposal is actually a reopening of the comment period for FDA's 1997 proposed rule entitled "Dietary Supplements Containing Ephedrine Alkaloids," which solicited comments, in pertinent part, on the safety of consuming below 8 mg per serving of ephedra supplements. 62 Fed.

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1 We have been informed by FDA officials that in reopening the ephedra-related docket, the agency will include within Docket 95N-0304 all ephedra-related information provided to the agency since the initiation of its ephedra review. Accordingly, it is our clear understanding that the official "administrative record" will include all materials and information provided to FDA in all of the ephedra-related administrative dockets - including, but not limited to, Dockets 95N-0304 (current proceeding), 00N-1200 (adverse event reports associated with the use of dietary supplements containing ephedrine alkaloids), and 01P-0396 (request that FDA ban the production and sale of all ephedra products). We officially incorporate by reference into this submission all of the materials and information contained in the above mentioned dockets.

2 In using the term "ephedra supplements," we are referring to the herb ephedra, or extracts thereof. This term is not intended to encompass synthetic ephedrine.

95N-0304 C3933

Reg. 30,678, 30,694 (June 4, 1997). FDA solicited comments because "[t]he evidence does not exist to establish a safe level," (id. at 30,694) and tentatively concluded that consuming ephedra supplements at a level of greater than 8 mg per serving "presents a significant and unreasonable risk of illness or injury ... and that, therefore, products that contain this or higher levels of ephedrine alkaloids are adulterated." Id. at 30,693.

On April 3, 2000, parts of this original proposal were withdrawn "because of concerns regarding the agency's basis for proposing a certain dietary ingredient level and a duration of use limit for" ephedra supplements. 65 Fed. Reg. 17,474 (Apr. 3, 2000). The concerns stemmed from the Government Accounting Office's (GAO's) examination of the scientific bases for the 1997 proposal, which found, among other things, that FDA needed more evidence than adverse event reports (AERs) to support the proposed dosing level and duration of use limit. 65 Fed. Reg. at 17,475; GAO, Dietary Supplements Uncertainties in Analyses Underlying FDA's Proposed Rule on Ephedrine Alkaloids (hereinafter "GAO Report") 24 (July 1999). GAO stated that the AERs "suffer[ed] from several problems" such as their questionable quality, and "FDA did not establish a causal link between the ingestion of ephedrine alkaloids and the occurrence of particular adverse events." GAO Report at 24.

On August 8, 2000, the United States Department of Health and Human Services (HHS), Office on Women's Health, held a public meeting to discuss the safety of dietary supplements containing ephedra alkaloids. The meeting was in response to a Federal Register Notice of April 3, 2000 that announced the availability of new AER's and established a new Docket No. 00N-1200. See 65 Fed. Reg. 43,021 (July 12, 2000). Following the meeting, the Office of Women's Health issued a summary report of the meeting, which did not conclude that ephedra supplements presented a significant risk to consumers. The report called for a systematic review of the literature of ephedra, as well as a consumer education campaign. See The Safety of Dietary Supplements Containing Ephedrine Alkaloids, Public Meeting August 8-9, 2000 Report (Aug. 2000). Simultaneously, FDA reopened the comment period for Docket No. 00N-1200 for FDA to consider the safety of ephedra supplements until September 30, 2000. See 65 Fed. Reg. 46,721 (July 31, 2000).

Almost six years have passed since the original proposal, and FDA has reopened the comment period to receive comments on "new scientific evidence [that] has come to light concerning health risks associated with the use of [ephedra] supplements." 68 Fed. Reg. 10,417 (Mar. 5, 2003). FDA would also like comments on whether "FDA should determine that [ephedra supplements] present a 'significant or unreasonable risk of illness or injury under conditions of use recommended or suggested in labeling, or if no conditions of use are suggested or recommended in the labeling, under ordinary conditions of use.'" Id. at 10,419. Nutraceutical submits these comments to show that

there is absolutely no basis for concluding that Nutraceutical's whole-herb ephedra supplement products present a significant or unreasonable risk as labeled, and that whole-herb ephedra supplements in general do not present a significant or unreasonable risk under conditions of use recommended or suggested in the labeling, under ordinary conditions of use.[3]

Nutraceutical manufactures ephedra supplements that contain whole-herb ephedra sinica.[4] The ephedra supplements are sold in bottles with 100 capsules or 180 capsules. Each of the two products instruct the consumer to take one capsule at a time, not to exceed two capsules daily for the ephedra sinica products. The ephedra products contain approximately 3.75 mg of naturally occurring ephedra alkaloids per capsule.[5] See Nutraceutical's product labels (copy attached). Nutraceutical's products have been sold for approximately 14 years, and, to Nutraceutical's knowledge, there have only been three adverse event reports involving these products during their marketing history, none of which provide evidence of a risk to consumers. There is also a lack of reported events for whole-herb ephedra products in general, and a lack of information in the published literature that these products present any health risk when properly consumed.

Therefore, there is no basis for determining that Nutraceutical's, or any manufacturer's, whole-herb ephedra dietary supplement presents a "significant or unreasonable risk of illness or injury under conditions of use recommended or suggested in labeling, or if no conditions of use are suggested in the labeling, under ordinary conditions of use." 21 U.S.C. § 342(f)(1)(A). Further, since no reports of heart attack,

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3 Nutraceutical agrees with the historic industry standards for ephedra products, both whole-herb and extracts, as exemplified by the American Herbal Products Association's Ephedra Trade Recommendation, and with comments submitted in the past to the various ephedra dockets as well as this docket supporting the safety and benefits of ephedra products when marketed according to these industry standards. The science shows that ephedra is safe at serving amounts of 25 mg of ephedrine alkaloids per serving and 100 mg per day, when labeled with appropriate warnings.

4 *Ephedra sinica* is also known by its Chinese name, ma huang.

5 Nutraceutical's ephedra supplements contain 375 mg of raw herb ephedra in each capsule. The average alkaloid content for ephedra sinica is 1.259 percent. See Cui JF, Niu CQ, Zhang JS. Determination of six Ephedra alkaloids in Chinese Ephedra (Ma Huang) by gas, Acta Pharmaceutical Sinica 26(11):852-7, 855 (1991). Thus, Nutraceutical's products contain approximately 3.75 mg of naturally occurring ephedra alkaloids per capsule.

stroke, seizure or deaths have been reported for these products, there is no scientific basis for the proposed warning on the principal display panel of these products. Nutraceutical is willing to update its labels to conform with the remainder of the proposed warning, which is very similar to the warning that the company currently employs for its ephedra products.

I. FDA First Must Define the Meaning of "Significant or Unreasonable risk of Illness or Injury Under Conditions of Use Recommended or Suggested in the Labeling, or ... Under Ordinary Conditions of Use."

Section 4 of the Dietary Supplement Health and Education Act of 1994 (DSHEA) amends section 402 of the Federal Food, Drug and Cosmetic Act (FDC Act), 21 U.S.C. § 342, to provide that a dietary supplement, or a dietary ingredient in a dietary supplement, shall be deemed to be "adulterated" if it:

> (A) presents a significant or unreasonable risk of illness or injury under -
>
> (i) conditions of use recommended or suggested in the labeling, or
>
> (ii) if no conditions of use are suggested or recommended in the labeling, under ordinary conditions of use;

In order to take regulatory action against a supplement, the "United States bears the burden of proof on each element to show that a dietary supplement is adulterated." 21 U.S.C. § 342(f)(1)(D). In its 1997 proposed rule on ephedra supplements, FDA stated that a dietary supplement would be adulterated because it "present[ed] a significant or unreasonable risk of illness or injury under conditions of use recommended or suggested in labeling" (62 Fed. Reg. 30,678, 30,693) by recommending or suggesting conditions of use "that would result in the intake of 8 mg or more in a 6-hour period or a total daily intake of 24 mg or more of ephedrine alkaloids." Id. at 30,678.

In order to enforce this determination in a United States court, the government must be able to prove that this dosage of ephedra supplements "presents a significant or unreasonable risk of illness or injury." However, the term is undefined in DSHEA, and FDA has not established any working definition of what constitutes a "significant risk" or "unreasonable risk." The first step in the process of determining whether any dietary supplement product meets this standard should be a rulemaking to establish a definition for the standard. It is therefore premature for the agency to attempt to engage in a determination of whether ephedra supplements in general present a "significant risk" or "unreasonable risk" to health, if indeed it would ever be possible to make such a determination for an entire class of products with different formulations and labeling.

Regardless of how FDA eventually defines the "significant or unreasonable risk of illness or injury" standard, given the long history of safe use and the lack of reports of adverse events for whole-herb ephedra products, despite widespread and very negative publicity concerning all ephedra products, there is no basis for a determination that the whole-herb products, such as Nutraceutical's ephedra products, present a "significant or unreasonable risk of illness or injury" under labeled or ordinary conditions of use.

II. Whole-Herb Ephedra Supplements In General Do Not Present a "Significant or Unreasonable Risk of Illness or Injury ... Under Ordinary Conditions of Use."

Nutraceutical's ephedra sinica supplements belong to a class called "whole-herb" ephedra supplements. Several species of ephedra, including ephedra sinica, have been safely used as a Chinese herbal remedy for more than 5,000 years without reports in the historic literature of significant adverse effects. In fact, some experts have called it "the oldest medicinal plant in continuous use." See Ephedra and Ephedrine for Weight Loss and Athletic Performance Enhancement: Clinical Efficacy and Side Effects. No. 76, Prepared for: Agency for Healthcare Research and Quality at 7, Feb. 2003 (hereinafter "RAND Report"). Ephedra has also been used for thousands of years in India in the treatment of bronchial asthma. See Varro E. Tyler, The Honest Herbal: A Sensible Guide to the use of Herbs and Related Remedies 119 (The Haworth Press 1993) (1982). In the 1930's, the alkaloid ephedrine was isolated and it began to be widely used in the United States as a nasal decongestant, a central nervous system stimulant, and a treatment for bronchial asthma. Id. The German Commission E has also approved a monograph for ephedra for certain uses. See The American Botanical Council, The Complete German Commission E Monographs Therapeutic Guide to Herbal Medicines 125 (American Botanical Council 1998).

Whole-herb products are different from extracts of ephedra because the products contain a certain mass or volume of the herb rather than a certain amount of a specified alkaloid or other compound. Nutraceutical's products contain the naturally occurring ratio of what are commonly referred to as "ephedrine alkaloids." Whole-herb ephedra is believed to be more slowly absorbed by the body than supplements formulated with standardized extracts. See Bill Gurley, Extract Versus Herb: Effect of Formulation on the Absorption Rate of Botanical Ephedrine from Dietary Supplements Containing *Ephedra* (Ma Huang), Therapeutic Drug Monitoring 22:497 (2000). The typical percentage alkaloid content of whole-herb ephedra is 1.259 percent total alkaloids. See Cui, Determination of six Ephedra alkaloids in Chinese Ephedra (Ma Huang) by gas at 855.

Several other companies manufacture and sell whole-herb ephedra supplements. A review of the AER's since 1993 shows that there is no evidence of any risk to consumers with whole-herb ephedra products when used according to "conditions of use recommended or suggested in labeling, or ... under ordinary conditions of use." There have been at most three AER's filed for whole-herb ephedra supplements other than those manufactured by Nutraceutical. Two can be dismissed because it is unclear what type of product the consumer was taking. See Food and Drug Administration ARMS # 10866; ARMS # 14435.[6]

The single report that is even potentially related to a whole-herb product other than a Nutraceutical product was an AER filed in 2000 by a 31-year-old male who took a "few sips" of Nature's Wonderland whole-herb ephedra tea. The consumer said he suffered his first anxiety attack an hour after taking a few sips of the tea, and continues to suffer from anxiety and anxiety attacks. The consumer stated that he had mild anxiety in social situations before he drank the ephedra tea, and was taking several medications including Amitriptylene, Risperdal, Tetracycline, and Naproxen. It is unclear from the report whether the consumer was taking Ativan at the time of the event or if it was prescribed after the anxiety attacks began. No medical records are included in this report. See FDA ARMS# 14435 (2000).

This report is typical of the vast majority of AERs on ephedra products in that it provides almost no information on which an assessment can be made as to whether ephedra might be causally linked to the reported event. Furthermore, this AER does not qualify as a "sentinel event" under the RAND study criteria. In reviewing the case reports, RAND classified a report as a "sentinel event" if it determined that there was "a potential role for ephedra or ephedrine in causing the event." See RAND Report at 30. In order to qualify as a sentinel event, there were several criteria and procedures that RAND followed. RAND did not consider anxiety attacks to be a sentinel event, and excluded as possible sentinel events cases of psychiatric symptoms in which patients had a history of psychiatric problems. They were classified as "inconclusive." Id. at 32.

A single report of an adverse event that, at best, could be described as "inconclusive" with respect to any link to ephedra consumption does not constitute evidence that whole-herb ephedra supplements present an unreasonable risk of illness or injury under conditions of use recommended or suggested in labeling, or ... under ordinary conditions of use." 21 U.S.C. § 342(f)(1)(A). Therefore, FDA cannot establish that such products are "adulterated."

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[6] FDA files contain a third report on a whole-herb product with a date of June 29, 1995 that has no ARMS #.

III. Nutraceutical's Ephedra Supplements Do Not Present a "Significant or Unreasonable Risk of Illness or Injury Under Conditions of Use Recommended or Suggested in Labeling, or ... Under Ordinary Conditions of Use."

A. Nutraceutical's whole-herb ephedra supplement products are well below the serving amounts proposed by FDA in 1997

As discussed above, Nutraceutical manufactures whole-herb ephedra sinica supplements that contain approximately 3.75 mg to 4 mg of naturally occurring ephedrine alkaloids per capsule. Each of the two products instruct the consumer to take one capsule at a time, not to exceed two capsules daily for the ephedra sinica products. If taken in accordance with the directions on the label, this amounts to a recommended dosing of 3.75 mg ephedra alkaloid per serving and 7.50 mg ephedra alkaloid per day. See Nutraceutical product label. Each capsule contains 375 mg of ephedra, which is consistent with the typical alkaloid content of approximately 1% for whole-herb ephedra supplements. See Cui, Determination of six Ephedra alkaloids in Chinese Ephedra (Ma Haung) by gas, at 855.

These doses of ephedra alkaloids are well below the extremely conservative standard proposed by FDA in 1997, and there is no evidence suggesting there is any risk associated with these products. In its 2000 Federal Register notice, FDA withdrew the proposed standard of adulteration because it did not have sufficient evidence to support the proposed serving amounts. 65 Fed. Reg. 17,474 (Apr. 5, 2000). If FDA cannot meet its burden of proof to show that serving levels of "8 mg or more in a 6-hour period or a total daily intake of 24 mg or more of ephedrine alkaloids" present a significant or unreasonable risk of illness or injury, then it also does not have sufficient evidence to determine that Nutraceutical's products are adulterated.

Furthermore, a report issued in December 2000 concluded that consuming 90 mg per day of ephedrine alkaloid was the upper limit No-Observed-Adverse-Effect Level (NOAEL) value for healthy adults. See Cantox Health Sciences International, Safety Assessment and Determination of a Tolerable Upper Limit for Ephedra, at x (Dec. 19, 2000) (hereinafter "Cantox Report"). This is far above the recommended servings of ephedra alkaloids for Nutraceutical's products. The Cantox Report was based on a critical review of clinical and nonclinical safety databases, published case reports, and AER data, and established a safe upper intake level for ephedrine alkaloids. See id. at 1. Similarly, the RAND Report of 2003 analyzed new evidence of the adverse consequences from clinical trials and case reports. The results of this study are consistent with the Cantox Report's determination of an upper limit. The RAND Report concludes that,

although there were a large number of AER's for ephedra supplements, "[t]he majority of FDA case reports are insufficiently documented to make an informed judgment about the relationship between the use of ephedra-containing dietary supplements and the adverse event in question." RAND Report at 203. The RAND Report supports the benefits of ephedra for weight loss as well as the safety of ephedra products, even though RAND concluded that additional studies should be conducted to help resolve widely publicized, but entirely speculative, concerns that have been caused by adverse event reports for products other than Nutraceutical's products.

B. There is no evidence that Nutraceutical's ephedra supplements represent <u>any</u> risk to consumers.

Nutraceutical has sold its ephedra supplement products since approximately 1988. During the 14 years of sales and marketing, there have only been three AER's to FDA for Nutraceutical's whole-herb ephedra supplements. <u>See</u> Food and Drug Administration, ARMS # 12837; ARMS # 11608; ARMS # 11780. Two of these reports can be dismissed due to clear abuse of the products, and one cannot be linked to ephedra. This does not provide evidence of any risk to consumers, much less a significant or unreasonable risk.

The first of the three FDA adverse event reports for Nutraceutical's whole-herb ephedra products occurred in 1995. A 50-year-old female was taking 2 capsules of the product each day and complained of feeling anxious and of a racing heart. This adverse event, however, cannot be linked to the ephedra because the woman had several pre-existing medical conditions. She was taking medication for depression and had a genetic enzyme deficiency. This event is not relevant to the product as currently labeled because it contains a prominent warning section on the product, which states that the product should not be taken concurrently with antidepressants. These pre-existing conditions, combined with the ephedra supplement, most likely produced the anxiousness and racing heart.

The second adverse event report occurred in 1996, when a 29-year-old female complained of tingling sensations in her arms and legs. There is insufficient information in this report, as with the vast majority of these reports, to make any assessment of whether the event was in any way related to ephedra consumption. However, the consumer did report that she was taking 8 to 10 capsules per day. This greatly exceeds the directions on the label, stating that a person should not exceed 2 capsules per day. This woman's adverse events, even if ephedra-related, are not a result of using the product as recommended or suggested in labeling. The woman was misusing the product.

Similarly, the third adverse event report described clear misuse of the product. A 31-year-old male reported feeling extreme tension, feelings of mania, and an alleged relapse of a cocaine addiction after taking Nutraceutical's ephedra sinica. The reporter began taking 1 pill per day. This dose gradually increased for one month until he was taking pills "all day long, every few hours and a couple at a time." See FDA ARMS# 12837. Eventually, the dose reached 20 to 25 capsules per day. Again, there is insufficient information in this report to make any assessment of whether the event was in any way related to ephedra consumption. In addition, this report illustrates a clear case of product abuse as well as drug abuse, and the adverse events, if in any way linked to ephedra, cannot be associated with using the product as recommended or suggested in the labeling.

It is clear that none of the three adverse event reports for Nutraceutical's whole-herb ephedra supplements can be used as evidence to show that the products present a significant and unreasonable risk of illness or injury under the "conditions or use recommended or suggested in labeling." In fact, there is no evidence to support the proposition that the products present any risk to consumers when they are used according to the directions on the label.

IV. There is No Scientific Basis for Requiring Whole-herb Products to Include the Warning that FDA has Proposed on the Principal Display Panel.

In its 2003 reopening of the comment period, FDA proposed a warning statement that should appear on the principal display panel (PDP) of the products. 68 Fed. Reg. 10,417, 10,419 (Mar. 5, 2003). The warning statement states in bold print that "Heart attack, stroke, seizure, and death have been reported after consumption of ephedrine alkaloids." Id. There is absolutely no need for such a warning statement on Nutraceutical's or other whole-herb ephedra supplements. FDA has not received any reports that whole-herb products have been associated with heart attack, stroke, seizure, or death. There is no evidence that whole-herb products are causally related to these events. Given the lack of evidence of any of these safety issues, such a warning statement on these products would be inappropriate and false.

If a warning statement is to be included on the PDP, it would be appropriate for Nutraceutical and other whole-herb ephedra supplements to state that the product "contains ephedrine alkaloids." The consumer would then be directed to the information panel, which would include the other warning statements proposed by FDA.

V. Conclusion

These comments show the lack of evidence of any risk associated with Nutraceutical's whole-herb ephedra sinica products. Whole-herb ephedra is believed to be absorbed at a slower rate than extracts. The recommended servings on Nutraceutical's labels are well below FDA's conservative standard from its 1997 proposed rule. Of the three adverse event reports filed for Nutraceutical's ephedra supplements since approximately 1988, two can be dismissed because the product was being misused, and the third cannot be linked to the ephedra. In examining other whole-herb ephedra supplements it is also evident that they present no risk to consumers. FDA cannot establish that Nutraceutical's whole-herb ephedra sinica supplements "present[] a significant or unreasonable risk of illness or injury under conditions of use recommended or suggested in the labeling," or that whole-herb ephedra products present this risk "under ordinary conditions of use."

FDA should issue a final rule with required warnings for ephedra products. The proposed warning for the principal display panel for ephedra products is misleading with respect to all ephedra products and is false with respect to whole-herb ephedra products, and therefore should be dropped or revised. Nutraceutical is willing to update its labels to conform to the remainder of the proposed warning label.

Respectfully submitted,

Nutraceutical Corporation

Stanley E. Soper
Vice President, Legal Affairs

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Supplement Facts

Serving Size 1 Capsule

	Amount Per Serving	% Daily Value
Ephedra (*Ephedra sinica*) (aerial)	375 mg	*
(Supplying 3.75 mg [1%] ephedra alkaloids per capsule)		

*Daily Value not established

OTHER INGREDIENTS: Gelatin Capsule and Magnesium Stearate.

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OTHER INGREDIENTS: Gelatin Capsule and Magnesium Stearate.

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