Docket No. 095N--0304

BEFORE

THE UNITED STATES OF AMERICA

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

THE AMERICAN HERBALISTS GUILD

ON THE PROPOSED RULE FOR

DIETARY SUPPLEMENTS CONTAINING *EPHEDRA* ALKALOIDS

UPON THE REOPENING OF THE COMMENT PERIOD

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Submitted April 7, 2003

1. PREAMBLE

1. The American Herbalists Guild (AHG) is a non-profit organization that represents professional practitioners of herbal medicine in the USA.

2 AHG professional members are elected by rigorous peer review and have extensive training and clinical experience in herbal medicine. Members include licensed practitioners such as Naturopathic physicians and Acupuncturists, as well as lay members - there being no license for herbalists in the USA at this time. AHG members are by definition experienced not only with medicinal plants, or herbal "medicines" as such, but also with the *practice* of using botanicals therapeutically i.e. herbal ***medicine (practice)*** using herbal ***medicines (remedies).***

3. AHG professional members operate entirely within the current legal and regulatory framework governing the availability of and access to botanical medicines. However the AHG also believes that the current regulatory framework in the USA, embodied in DSHEA 1994, fails to embody a coherent description of traditional herbal medicines. By subsuming botanicals within its over inclusive definition of "dietary supplements", the Act confounds crude medicinal herbs as used in herbal medicine with manipulated commercial products, concentrates, components or combination products which have no established record of safety in traditional use, nor indication for derived from empirical traditional practice. The AHG views the current problematic status of *Ephedra* and *Ephedra* alkaloid containing supplements to be an inevitable result of the underlying problems of definition embedded within DSHEA.

4. The AHG understands that comments are requested on matters of interpretation of the current regulations regarding the available data on *Ephedra* products, their safety, indicated usage, and labeling, not upon the regulations themselves. However the issues surrounding *Ephedra* safety as currently framed, including the recent RAND report, derive from the current regulatory context and cannot be commented upon without some contextualization.

5. Restriction of public access to the crude herb *Ephedra sinica*, and extracts thereof, could, under the current legislative framework, also prevent AHG professionals, Licensed Acupuncturists, Naturopathic physicians and other healthcare professionals from access to the herb unless specific exemptions are made.

6. The AHG therefore welcomes the re-opening of the comment period on the proposals in the Federal Register regarding *Ephedra* (Docket No 95N-0304) and the opportunity to present the viewpoint of professional herbalists in the USA regarding *Ephedra sinica* and the dietary supplements containing *Ephedra* alkaloids.

2. SUMMARY OF THE AMERICAN HERBALIST GUILD GENERAL POSITION ON *EPHEDRA SINICA*

1. *Ephedra sinica* (Ma Huang) is a traditional herbal medicine that has an established history of safe clinical usage in East Asian and Western herbal medicine.

2. "*Ephedra*" properly refers to the dried aerial parts of the medicinal species, or crude extracts thereof, not to its isolated alkaloidal constituents.

3. There is no credible review to date which analyzes safety data (whether experimental, clinical or derived from pharmacosurveillance sources), including the RAND and CANTOX reports, that takes systematic account of the terminological confusion between the crude herb, isolated ephedrine, and *Ephedra*/ephedrine plus caffeine combination products. Rather, all these literary sources compound the problem.

4. Traditional usage of *Ephedra sinica* (Ma Huang) regularly involves combination with other herbs, but never stimulants.

5. *Ephedra sinica* is safe when used for traditional indications at the established therapeutic doses.

6. The established therapeutic dose range of *Ephedra sinica* in herbal medicine delivers 60 -90 mg total alkaloid per day (adults). There is broad agreement between traditional Chinese formulae, western herbal doses, and recommended doses of OTC preparations in terms of total daily alkaloid intake.

7. Doses of ephedra alkaloids in excess of the therapeutic dose range, whether delivered via crude herb, concentrated extracts or isolated alkaloids, do have the potential to induce adverse effects.

8. "Weight loss" and "athletic performance" are not traditional indications for the use of *Ephedra* - traditional indications are centered around the use of the herb for febrile and catarrhal respiratory conditions. Arguably, from a clinical natural medicine perspective, obesity is more likely to be a contraindication rather than an indication for use of *Ephedra*.

9. The lobby of sections of the natural products industry for the weight loss indication of *Ephedra* cannot readily be dissociated from their interest in the ($6.8billion) market for ephedra weight loss products while the lobby against "Ephedra" is often ill informed and politically motivated.

10.The scope and magnitude of *Ephedra* safety and the problem of herbal adverse effects in general should be seen in the larger context of the outstanding safety record of herbal medicines compared to that of licensed pharmaceuticals.

3. THE AMERICAN HERBALIST GUILD GENERAL POSITION ON *EPHEDRA*

The general position of the AHG on *Ephedra* is summarized in the following points.

[Note: The capitalized "*Ephedra*" is used to designate crude herb of medicinal species of the *Ephedra* taxon as defined below].

1. *Ephedra sinica* (Ma Huang) is a traditional herbal medicine that has an established history of safe clinical usage in East Asian and Western herbal medicine.

Currently recognized medicinal species of the genus are *E. sinica* Stapf., *E. equisetina* Bunge., *E. intermedia* Shenk and CA Meyer., (f. *Ephedra*ceae) all of which contain *Ephedra* alkaloids and are regarded as medicinally (and commercially) interchangeable.

Traditional indications for medicinal *Ephedra* species include febrile and congested catarrhal conditions of the upper respiratory tract, with diaphoretic, diuretic, and cardiotonic actions.

2. "*Ephedra*" properly refers to the dried aerial parts of the medicinal species, or crude extracts thereof, not to its isolated alkaloidal constituents.

2i. There is a persistent terminological confusion in the current literature, perpetuated by all parties concerned including FDA and DHHS and which pervades the current medical literature including the recent RAND report. This confusion implies the crude herb is interchangeable with ephedrine, the alkaloid, or even with commercial dietary supplements containing isolated *Ephedra* alkaloids in combination with other agents, such as caffeine.

2ii. The distinction is not academic, but axiomatic. *Ephedra sinica* crude herb and crude herb extracts have different pharmacological and medicinal characteristics than the purified isolated alkaloids in isolation.

- *Ephedra* contains catechin tannins such as (-)epicatechin (EC) and (-) epigallocatechin (EGC), catechin and gallocatechin. These polyphenolics, much studied as constituents of green tea, have antioxidant effects, hypolipidemic effects, cause NO mediated vasodilation, have antithrombotic, anti-inflammatory, antidiabetic, and antiproliferative and chemoprotective effects.

- *Ephedra* contains a volatile oil, composed largely of monoterpenes such as terpinol and cineole. These are well known as constituents of Eucalyptus and Juniper that have significant pharmacological actions at bronchial, respiratory and urinary epithelia. *Ephedra* also contains various phenolic acids, especially cinammic acid and derivatives that are common in the

balsams, well known for their respiratory effects.

- The medicinal Ephedraceae contain the characteristic phenylethylamine alkaloids, in amounts that vary from >1.0% and which can exceed 2%. The predominant alkaloid is (-)-ephedrine, which occurs alongside (+)-pseudoephedrine and their corresponding nor- and methyl- derivatives. These alkaloids all are indirect sympathomimetics, each alkaloid has, in a small degree, differing pharmacokinetic and pharmacodynamic properties, e.g. the nor- derivatives appear to be more centrally stimulating. The pharmacology of their action at the adrenoreceptor subtype level is not well understood, in part because the molecular biology of these receptor-sub types is currently still being unraveled. However, in general the *Ephedra* alkaloids are relatively non-specific in their effects with regard to adrenoreceptor subtypes, and in mainstream pharmacotherapy more receptor-selective adrenergic agonists are generally preferred to minimize general adrenergic side effects.

- This overall **combination** of constituents determines the medicinal effects of the crude herb. The total alkaloid content may vary by up to 100%, and the profile of component alkaloids varies between species, plant parts and season. Whilst the alkaloids indeed dominate the activity of the plant, its pharmacodynamics cannot be reduced to the properties of a single alkaloid alone, nor can the other constituents be disregarded.

- In parenthesis, it should be noted that in Chinese medical usage, a distinction is also made between the stems of the plant, *Ma Huang*, and the root, *Ma Huang gen.* The roots contain dimeric flavonols and macrocyclic alkaloids not found in the aerial parts, and in Chinese medicine the root is antisudorific, whilst the stem is diaphoretic – essentially opposite actions. The corollary being, as always with medicinal plants, that it is necessary to identify the plant part used as medicine.

2iii. The following categories are therefore quite distinct and rationally need to be considered as such in technical, scientific, medical and regulatory contexts:

- Isolated *Ephedra* alkaloids, (the phenylethylamines (-)-ephedrine, (+)-pseudoephedrine, their nor- and methyl, derivatives their optical isomers and salts of these compounds).

- Crude herb and extracts of crude herb of medicinal *Ephedra* taxa (as defined above) containing naturally occurring alkaloids and other compounds without manipulation, concentration, or adulteration such as in decoctions or crude herb extracts.

- Extracts of *Ephedra* that are concentrated, manipulated or adulterated such that the naturally occurring proportions and/or quantities of ephedrine

alkaloids are changed.

- Combination "ephedra/ephedrine products" variously including any of the above with any other agents, herbal or otherwise for example:

  Caffeine, caffeine containing herbs (e.g. *Guarana, Cola*), or concentrates of caffeine containing herbs; salicylates, either in the form of ASA, (aspirin) or salicylate containing herbs (e.g. willow bark) or concentrates of salicylate containing herbs; synephrine and accessory nutrients such as chromium picolinate, L-carnitine, CoQ10 and B vitamins.

- Legitimate traditional herbal medicinal combination formulations such as "Minor Blue Dragon" or other standard Ma Huang containing Chinese formulae.

2iv. Confusion is compounded by regulatory differentiation between isolated (-)-ephedrine concentrated from crude herb sources and laboratory synthesized (+)-ephedrine. The former is a "dietary ingredient" while the latter is a listed (controlled) chemical compound (also a marker for identifying adulteration). Addition of the former to an *Ephedra* dietary supplement product containing Ma Huang would simply require adding an "ingredient" to the label; addition of the latter would constitute illegal "adulteration" of the dietary supplement.

3. The AHG maintains that there is no credible review to date which analyzes safety data (whether experimental, clinical or derived from pharmacosurveillance sources), including the RAND and CANTOX reports, that takes systematic account of the terminological confusion between the crude herb, isolated ephedrine, and *Ephedra*/ephedrine plus caffeine combination products. Rather, all these literary sources compound the problem.

The RAND report conclusions exemplify both the logical and terminological confusions. Even the first page of the conclusions (p201) uses ALL of the following terms: "*ephedra*", "*herbal ephedra*", "*ephedra without caffeine containing herbs*", "*ephedra with caffeine containing herbs*", "*ephedra containing dietary supplements with caffeine containing herbs*", "*ephedra and herbs with caffeine*", "*ephedrine*", "*ephedrine plus caffeine*".

The RAND meta-analysis refers to one study (Donikiyan and colleagues, unpublished, 2002) that purports to examine "ephedra" alone vs. placebo; this study is mentioned also in the conclusions. In fact the preparation used in this study contained 450 micrograms of chromium picolinate per dose, and therefore cannot be considered a crude herb extract vs. placebo at all. This failure to identify and disclose all the ingredients of the product lacks scientific rigor and is inevitably misleading.

4. Traditional usage of *Ephedra sinica* (Ma Huang) regularly involves combination with other herbs, but never stimulants.

In all extant traditions of herbal medicine, East Asian and Western, that incorporate *Ephedra* use, it is almost never used as a single agent. In medicinal use, it is considered to have stimulating properties, and is never combined with herbs that also have stimulant properties such as caffeine containing herbs (*Coffea, Paullinia, Cola*). In East Asian herbal use, *Ephedra* is characterized by its warming and diaphoretic qualities, and is therefore combined with herbs that moderate this warming aspect, or which mitigate its stimulatory tendencies. This specifically excludes combination with stimulant herbs. The common proportion of *Ephedra* in such formulations is rarely more than 15% of total herb. Professional herbalists thus consider the traditionally prepared combination products to have a much greater margin of safety than ephedrine isolates or combination caffeine products.

5. *Ephedra sinica* used for traditional indications at the established therapeutic doses is completely safe.

To our knowledge, there is not a single published report in the medical or toxicological literature recording serious adverse effects resulting from the crude herb or crude extracts of the medicinal *Ephedra* species used within the therapeutic dose range for traditional medical indications.

This point cannot be overemphasized. Every literature review, including RAND, CANTOX or the recent comprehensive review by McKenna and colleagues cited in RAND, refers to "ephedra/ephedrine combination products" i.e. combinations with other stimulants, or the effects of isolated alkaloids, usually ephedrine (this being more studied than the others). The safety record of the crude herb used at therapeutic doses is exemplary, and at complete variance with the "bad press" that has become associated with it.

The process whereby such a "bad press" becomes attached to a botanical because of commercial-industrial exploitation of concentrates or isolated derivatives rather than the crude herb is familiar to those who are fluent in the science and care to follow the literature. Licorice root is a classic example, although lacking in the market profile enjoyed by *Ephedra* products its notoriety is nonetheless an established "fact" in the medical literature despite a complete absence of adverse effect reports concerning the medicinal herb at therapeutic doses – all reports referring to concentrated commercial licorice extracts and flavorings in products such as chewing tobacco.

6. The established therapeutic dose range of *Ephedra sinica* in herbal medicine delivers 60 -90 mg total alkaloid per day (adults). There is broad agreement between

traditional Chinese formulae, western herbal doses, and recommended doses of OTC preparations in terms of total alkaloid.

OTC use of ephedrine salts in commercial OTC preparations, indicated for nasal congestion, deliver up to 25mg every 4 hours with a suggested maximum of 150mg alkaloid daily.[1] Meanwhile, PDR recommendations for maximum dose of pseudoephedrine hydrochloride in nasal decongestant products (such as e.g. Sudafed™) suggest a daily adult maximum of 240 mg alkaloid over a twenty-four hour period.

Traditional Chinese standard formulae (such as Minor Blue Dragon, Ma Huang C Decoction) typically deliver 60-90 mg alkaloid per day, (assuming that *Ephedra* alkaloids are present at concentrations of >1% w/w in the crude herb). Ma Huang is usually <15% of such formulae.

This broad therapeutic dose range is confirmed by numerous international authorities in western herbal medicine. The German Commission E gives the maximum daily dose at 300mg total *Ephedra* alkaloid, which is higher than might be expected from this source, which is normally considered conservative in terms of safety issues.

7. Doses of *Ephedra* alkaloids in excess of the therapeutic dose range, whether delivered via crude herb or concentrated extracts, do have the potential to induce adverse effects.

From a clinical perspective, the potential for sympathomimetic agents to cause autonomic side effects is both plausible and predictable; no responsible or competent clinician would think otherwise. The potential for interaction with other adrenergic agonists, with MAO inhibitors, and exogenous catecholamines is also very probable. Similarly, contraindication in specific conditions, such as hypertension and cardiac dysrhythmia, is also a corollary of the known pharmacology of these compounds. Herbal medicine is a context based patient-centered discipline and herbal combinations are administered on a case-by-case basis recognizing each individual as unique. Despite the general safety of traditional combinations of *Ephedra* used at the therapeutic dose range, professional herbalists monitor for side effects and adjust dosage accordingly in sensitive individuals who exhibit symptoms of adverse effects.

8. "Weight loss" and "athletic performance" are not traditional indications for the use of *Ephedra*. Traditional indications are centered on the use of the herb for febrile

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[1] HHS OTC monograph 21 CFR Ch 1 para 341.76 "Labeling of bronchodilator products" 4.1.99 edition.

and catarrhal respiratory conditions. Arguably, from a clinical natural medicine perspective, obesity is more likely to be a contraindication rather than indication for use of *Ephedra*.

8 i. Medicinal herbal indications are incrementally established by empirical clinical use over centuries, sometimes millennia. They are generally not defined by scientific studies, although modern scientific research may often confirm or illuminate an already established traditional indication.[2]

8 ii. Extrapolation from the known pharmacology of herbal constituents may *suggest* non-traditional therapeutic uses of an herb. Commercial promotion of these suggested uses by marketing of dietary supplements does not constitute validation of these indications.

- Echinacea for example is traditionally indicated for boils and abscesses, or for snakebites. As its immunomodulating properties were studied, the use of echinacea as a cold and flu remedy became promoted by the supplement industry. Scientific support of echinacea for colds and flu is in fact quite weak, and the majority of herbalists still regard it as a lymphatic system agent with short term modulating effects on cell mediated immunity. The significant point being that the debate in the medical and popular literature about "does echinacea work?" i.e. for "colds and flu" is simply an artifact of a mistaken presumption by both the investigating researchers and journalists that the market driven "indications" suggested by the US natural products industry are the traditional indications of the herb. There are no published studies on echinacea for topical bites, but its ability to deal with serious necrotoxic venomous spider and snakebites is well established among modern herbalists. In other words, although onset of a cold or flu may be a plausible indication for echinacea based on its immuno-modulatory pharmacology, it does not mean that "echinacea for colds" is an appropriate indication for the herb.

8 iii. Not only is the overwhelming majority of adverse effect data (See 3 above) based upon combination products but *all* the trials used to support the weight loss indication meta-analysis in the RAND report were similarly based upon combination products, the majority being ephedrine in combination with caffeine and other stimulants. Not one study single study was based upon the use of crude herb.

8 iv. Nonetheless, due to the thermogenic and lipolytic characteristics of the *Ephedra* sympathomimetic amines, coupled with some central anorectic effects, the demonstration of a moderate effect on weight loss is to be expected given the known pharmacology of these alkaloids.

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[2] There are perhaps a very few arguable exceptions to this generalization such as the European research into Ginkgo flavonoids that developed the western herbal use of Ginkgo leaf as opposed to the traditional Ginkgo seed of TCM.

8 v. Thermogenic agents typified by the *Ephedra* alkaloids are not approved for weight loss, either as OTC or prescription drugs. However, these alkaloids are approved for use in respiratory OTC and prescription products. Sensible medical use as currently approved appears to corroborate traditional indications.

8 vi. While ephedrine alkaloid containing products may promote modest weight loss, and while we recognize that even modest weight loss can represent a significant health benefit, AHG professional herbalists do not consider this a sensible approach to a long-term, sustainable weight loss program. Sustained weight loss would either require dietary and lifestyle modifications, or chronic consumption of ephedrine alkaloid containing weight loss products, the latter which is contraindicated by traditional use standards.

8 vii. Because obese populations are predisposed (by definition) to higher risk of cardiovascular disease, we consider such populations to be at increased risk for potential ephedrine alkaloid side effects. The use of such agents is also associated with other undesirable side effects, including the tachyphylaxis (habituation or induced tolerance) that results from prolonged exposure, as well as undesirable psychological symptoms.

8 viii. Obesity is a serious public health problem affecting significant numbers of the population in the USA, with direct impact on morbidity and mortality statistics. The problem of obesity has a multifactorial cultural, psychological, dietary, lifestyle and pharmacogenetic etiology. "Popping fat burner stimulants" is seen by the AHG and most natural healthcare professionals more as part of the problem, not part of the solution. Arguably, from a clinical perspective, obesity is more likely to be a contraindication rather than indication for use of *Ephedra*.

8 ix. With regard to "athletic performance enhancement", not only is there no significant scientific support for this non traditional use of *Ephedra*, but the International Olympic Committee and most international sporting authorities define *Ephedra* alkaloids as prohibited stimulants. Athletes are disqualified even if these compounds were ingested unknowingly as OTC decongestant ingredients. Stimulant abuse in sports has been associated with numerous tragic serious adverse events related to drug abuse, usually sudden cardiac death. Promotion of "*Ephedra* performance products" in this market is unjustifiable on numerous counts and should be prohibited.

9. The lobby of sections of the natural products industry for the weight loss indication of *Ephedra* cannot readily be dissociated from their interest in the ($6.8billion) market for ephedra weight loss products while the lobby against "Ephedra" is often ill informed and politically motivated.

Industry organizations such as AHPA present a well-informed perspective on the

issues of *Ephedra*. The problems of ephedra product regulation are created by the current market for weight loss dietary supplements and the legislation that enables it. The AHG believes that clinical perspectives of herb professionals and those of natural product manufacturers should be closely aligned, for example in the development of and implementation of appropriate product characterization and appropriate claims review. Many AHG professional members depend on the ability of AHPA member companies to supply high quality, reliable, and safe crude herb extract. The AHG maintains that increased liaison and communication between the natural products industry, clinical practitioners, and regulatory authorities on matters relating to botanical medicines is desirable.

The AHG is particularly critical of those sections of the medical community, consumer watch dogs, various organizations and individuals including politicians, who call for sweeping restrictions on "*Ephedra*" (often along with attacks on all dietary supplements and botanicals), yet who demonstrate a lack of familiarity with either the technical, pharmacological, medical or public health and regulatory issues involved. The AHG considers this lobby to often have parochial agendas, ranging from political opportunism to conservative opposition to CAM (complementary and alternative medicine) and its tools, including botanicals.

10. The scope and magnitude of *Ephedra* safety and the problem of herbal adverse effects in general should be seen in the larger context of the outstanding safety record of herbal medicines compared to licensed pharmaceuticals.

The AHG maintains that the magnitude of the threat to public safety posed by the sum of all available botanical medicines is of minor significance compared to the number of serious adverse events, including deaths, among the US population due to non error related medication causes, estimated by various authorities to be at a figure of well over 100,000 deaths per anum. (Brown SD and Landry FJ. *South Med J* 2001;94(4):370-373; Lazarou J, et al. *JAMA* 1998;279(15):1200-1205)

The magnitude and scope of the *Ephedra* product safety problem, and of botanicals in general, needs to be contextualised within the larger picture of the extra-ordinarily good safety record of herbal medicines compared to pharmaceutical drugs approved by the FDA.

4. DOCKET 95N-0304: SPECIFIC COMMENTS OF THE AMERICAN HERBALIST GUILD

The DHHS has requested specific comments *"on the new evidence of public health risk associated with Ephedra"* and *"on whether the currently available evidence and medical literature present a 'significant or unreasonable risk of illness or injury' from dietary supplements containing Ephedra"* and upon a *"strong new warning label on any Ephedra products that continue to be marketed"*

Thus the specific comments of the AHG, derived from the foregoing general position on *Ephedra* are as follows:

1. The AHG contends that there is in fact no *"new evidence"* of public health risk associated with medicinal *Ephedra* species crude herb or extracts used at therapeutic doses for traditional indications.

The RAND report meta-analysis does not include a single study of *Ephedra* crude herb vs. placebo for weight loss or athletic performance since there is none. Similarly the adverse event data from the various sources in the RAND document (Medwatch, Metabolife files, clinical trial statistics) do not constitute "new evidence" about *Ephedra*, but merely reanalyze existing data, the quality of which has been critically reviewed previously, and none of which relates to the crude herb. Furthermore the RAND report persistently perpetuates the confusion of terminology relating to "ephedra" and the various products containing ephedra alkaloids, and to combinations with caffeine or other agents.

The AHG urges that a consistent terminology be adopted by the FDA and those medical and scientific authorities and investigators involved in the area, whereby inconsistent use of the term "ephedra" is replaced either by the term "*ephedrine alkaloid containing products*" as opposed to "*Ephedra sinica*" or crude extracts thereof, to distinguish the various manipulated dietary supplement products from the crude medicinal herb. Specific alkaloids should be referred to by their chemical name. Rationally, data deriving from investigations on different products should be identified as relating to the product concerned, should identify and quantify all the ingredients, and should not assume interchangeability with different preparations.

2. The AHG does not concur that weight loss or athletic performance enhancement are valid or traditional indications for *Ephedra sinica*. However the AHG considers there are inevitable risks associated with using *ephedrine* alkaloid containing products alone or in combination with other stimulants, in certain populations or individuals for such purported indications.

Quantifying *"significant or unreasonable risk of illness or injury"* requires

contextualization, including details of the exact nature of the preparation, the dose and duration of administration, the indication for which it is taken, the specifics of the individual case, and whether or not the administration is supervised or monitored by a healthcare practitioner. The level of risk will thus depend to a degree on the "appropriateness" of use.

The AHG considers that the public availability of *Ephedra*/ephedra alkaloid plus caffeine type combination products, and their promotion for weight loss and athletic enhancement constitutes inappropriate use which can reasonably and plausibly be predicted to generate a significant incidence of adverse effects, including a proportion of serious adverse effects in at-risk individuals, which is not the case with appropriate use of *Ephedra sinica* or crude extracts used for traditional indications at therapeutic doses.

3. The AHG concurs that a (strong) "new warning label" is desirable for any publicly available product that contains *Ephedra sinica*, including the crude herb.

Such warning labels would not be necessary for crude herb product distributed to healthcare professionals, including AHG professional members. In this regard, the AHG is not making extensive verbiage recommendations for public warning labels or about how "strong" they should be. However, logically, the medical warnings and contraindications should correspond to those currently applied to OTC medications containing ephedra alkaloids, the maximum dose of total alkaloid should correspond to the OTC established limits, and the labels would ideally include a clear statement that ephedra alkaloids cannot be recommended for weight loss.

4. The AHG urges the FDA to consider in future the separation of herbs and botanicals into an additional regulatory category such as "traditional herbal medicine".

The current legislative definition of dietary supplement under DSHEA 1994 "is defined as: 1. A product other than tobacco intended to supplement the diet that bears or contains one or more of the following dietary ingredients: * a vitamin; * a mineral; * **an herb or other botanical;** * an amino acid; * a dietary substance for use by man to supplement the diet by increasing the total dietary intake; or * **a concentrate, metabolite, constituent, extract, or combination of the above** listed dietary ingredients." (our emphasis).

The AHG urges the FDA to consider in future the separation of herbs and botanicals into a separate category such as "traditional herbal medicine". This would create a more appropriate and sophisticated regulatory armamentarium for distinguishing between say, ephedrine alkaloids and *Ephedra sinica*, and hence a more rational, effective and incisive means of protecting public safety.

Such a scheme for botanical medicines is supported by the World Health Organization. Moreover, such systems have been in place throughout Europe for

decades and currently there is a unified European Union traditional medicines proposal under development. We believe such a system is the most appropriate manner for the sale and use of herbs as medicines and represents the most rational approach by which to maximize the potential of their benefit to human health and to insure public safety. This system has been adopted by numerous countries, including Canada, Australia, the UK and other EEC members. While there are some minor national differences of interpretation, the essence of the matter is that crude medicinal herb and crude herb extracts with traditional indications are made available because of established safety record in traditional indications unless modern investigation and review deems otherwise.

Crude herb extracts which are concentrated (logically those concentrated beyond 1:1) and extracts whose composition has been manipulated, or adulterated in any way cannot legitimately claim safety on the basis of established use nor claim traditional indications for their use. These products are phytopharmaceuticals distinct from crude herb, and cannot reasonably be considered exempt from regulatory requirements to demonstrate safety or efficacy by virtue of their relationship to crude herb.