

ULLMAN, SHAPIRO & ULLMAN, LLP

COUNSELORS AT LAW

299 BROADWAY, SUITE 1700

NEW YORK, NY 10007

TEL. (212) 571-0068

FAX. (212) 571-0424

www.usulaw.com

usu@usulaw.com

WASHINGTON AFFILIATE
JAMES M. JOHNSTONE
1776 K STREET, NW
WASHINGTON, DC 20006

LONDON AFFILIATES
WEDLAKE BELL
16 BEDFORD STREET
COVENT GARDEN
LONDON WC2E 9HF
ENGLAND

E.U. CORRESPONDENT
LAFILL VAN CROMBRUGGHE
& PARTNERS
VOSSENDREEF 6 BUS 1
B-1180 BRUSSELS,
BELGIUM

ROBERT ULLMAN
STEVEN SHAPIRO*
MARC S. ULLMAN

SETH A. FLAUM*^o

TRADEMARK COUNSEL
DENNIS H. CAVANAUGH

BUSINESS & TECHNOLOGY COUNSEL
IRA R. HECHT*^Δ

OF COUNSEL
IRVING L. WIESEN

* ADMITTED IN NY & NJ
^o ADMITTED IN MD & DC
^Δ ADMITTED IN FL
[†] CPA

April 7, 2003

VIA EXPRESS MAIL

Dockets Management Branch
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: Docket No. 095N-0304

Dear Sir or Madam:

The attached comments are submitted on behalf of NVE Pharmaceuticals, Inc. regarding FDA's proposed rule for dietary supplements containing ephedra alkaloids.

Respectfully submitted,

ULLMAN, SHAPIRO & ULLMAN, LLP

Marc S. Ullman,

Seth A. Flaum,
Vanessa Riviere (awaiting admission
in New York and New Jersey),

Attorneys for
NVE Pharmaceuticals, Inc.

95N-0304

C3972

BEFORE

THE UNITED STATES OF AMERICA

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

COMMENTS OF

NVE PHARMACEUTICALS, INC.

ON THE PROPOSED RULE FOR

DIETARY SUPPLEMENTS CONTAINING EPHEDRA ALKALOIDS

DOCKET NO. 095N-0304

SUBMITTED BY

ULLMAN, SHAPIRO & ULLMAN, LLP

April 7, 2003

EPHEDRA
Safe When Used Responsibly

I.	EXECUTIVE SUMMARY	1
II.	WHAT IS EPHEDRA?.....	3
A.	EPHEDRA IS AN HERB	3
B.	WHAT IS EPHEDRINE?.....	5
III.	WHAT IS EPHEDRA USED FOR?.....	6
A.	HISTORY OF USE	6
1.	Chinese Medicinal Purposes.....	6
2.	History of Use in Weight Loss.....	7
B.	EXTENT OF USE	7
IV.	FDA’S REGULATION OF EPHEDRA (PRIOR AND CURRENT ISSUES).....	8
A.	FDCA / DSHEA	8
B.	1997 PROPOSED WARNINGS AND FORMULATION CHANGES (“1997 PROPOSED RULE”).....	9
1.	Government Responses to FDA Proposed Rules.....	10
a)	U.S. Small Business Administration (SBA) - Office of Advocacy; Comments.....	10
b)	U.S. General Accounting Office (“GAO Report”).....	10
2.	FDA Withdraws Much of the Proposed Regulation.....	11
3.	U.S. Department of Health and Human Services Public Meeting on Ephedra Safety (August 2000)	12
C.	2003 PROPOSED RULE	13
1.	New Warning.....	13
2.	No Formulation Issues Named.....	14
3.	No Preemption Issue Is Addressed	15
a)	State and Local Regulation of Ephedra	15
4.	FDA Rhetoric Unfounded.....	16
a)	Media Distortion of the Safety of Ephedra	16
(1)	Recent Adverse Event in the News.....	17
(a)	Steve Bechler	17
(b)	Korey Stringer.....	18
(c)	Anne Marie Capati.....	18
D.	THE RAND REPORT	19
1.	Introduction.....	19
2.	Common Terminology Used in Clinical Studies vs. RAND Terminology	19
a)	Adverse Events vs. Side Effects	19
b)	Define Expected Event	20
(1)	Expected Events of Ephedra Supplements	20
(a)	Weight Loss – Loss of Appetite.....	20
(b)	Energy.....	20
(c)	Combination Products.....	20
c)	Define Side Effect.....	21
(1)	Known Side Effects from Ephedra	21
(2)	Known Side Effects from Caffeine.....	21
d)	Define Adverse Event.....	22
e)	Different Terminology Used by RAND	22
(1)	“Adverse Event”	22

(2)	“Serious Adverse Event”	23
(3)	“Sentinel Event”.....	23
(4)	“Possible Sentinel Event”	24
(5)	“Probably Not Related”	24
3.	Findings.....	24
a)	Efficacy Findings in Weight Loss.....	24
(1)	What Data Did RAND Analyze?	24
(2)	Ephedra v. Placebo.....	26
(3)	Ephedra Plus Caffeine v. Placebo	26
b)	Safety Findings	27
(1)	Clinical Studies.....	27
(2)	Case Reports	28
(3)	FDA Misrepresents Safety Data	29
c)	Dosage Findings.....	30
4.	Issues Relating to RAND Safety Analysis.....	30
a)	Methods and Safety Conclusions.....	30
b)	Specific Serious Event Reports Cited by RAND.....	31
(1)	Case Report #1 (FDA/Ephedrine).....	31
(2)	Case Report #2 (FDA/Ephedrine).....	32
(3)	Case Report #3 (FDA/Ephedrine).....	32
(4)	Case Report #4 (FDA/Ephedra).....	32
5.	No Support that Ephedra is an Unreasonable Risk.....	33
6.	FDA’s Failure to Acknowledge Benefits for Weight Loss and Other Health Benefits.....	34
a)	Significant Public Health Benefit	35
b)	More Effective than Some Prescription Drugs	37
c)	No OTC Alternative.....	37
d)	FDA Misrepresents Efficacy Data.....	37
E.	OTHER EFFICACY STUDIES OF COMMERCIAL PRODUCTS	38
V.	EPHEDRA IS SAFE WHEN USED AS DIRECTED – ADDITIONAL DATA	39
A.	STUDIES AND EXPERT REPORTS	39
1.	Ephedra Education Council (EEC) Expert Panel Report.....	39
2.	The Cantox Report: Safety Assessment and Determination of a Tolerable Upper Limit for Ephedra.....	40
3.	The Harvard/Columbia Study: Herbal Ephedra/Caffeine for Weight Loss: A 6-Month Safety and Efficacy Trial	41
4.	The Greenway Article: The Safety and Efficacy of Pharmaceutical and Herbal Caffeine and Ephedrine Use as a Weight Loss Agent	41
5.	Summary of Incidence of Seizures, Strokes, and Myocardial Infarctions in the Population and Estimations of Risk in the Population from Ephedra Products (Stephen E. Kimmel, M.D.).....	42
6.	Ad Hoc Committee on Safety of Ma Huang (Dr. Dennis Jones; Herb Research Foundation).....	42
B.	REFERENCE TEXTS.....	43
VI.	AHPA’S ROLE	43
A.	INTRODUCTION	43
B.	HISTORY OF AHPA RE: EPHEDRA.....	44
1.	March 1994	44

2. January 1995	44
3. September 1995	44
4. January 1996	44
5. January 2000	45
6. September 2000	45
C. AHPA’s 2000 PETITION TO FDA	45
VII. POSITION WE SUPPORT	47
A. WE WOULD NOT OPPOSE THE ADOPTION OF STRICT WARNINGS AS LONG AS THEY ARE BASED IN TRUE SCIENCE AND NOT POLITICS.....	47
1. FDA’s Proposed “Back Panel” Warning	47
a) Proposed Modifications	47
(1) Medical Conditions.....	47
(2) Usage.....	47
(3) Health Care Provider.....	48
b) Creative Labeling.....	48
2. FDA Proposed Black Box Warning – Front	48
a) Not Justified	48
(1) Examples of Products with Black Boxes	49
(a) Nolvadex	49
(b) Hormone Replacement Therapy Drugs	49
b) Modified PDP Statement	49
3. Call for National Uniformity	49
4. Call for Responsible Marketing and Education	50
5. Strict Enforcement using DSHEA	50
a) Ephedra Is Regulated	50
b) Regulatory Status Distorted by Media.....	51
c) DSHEA Is Not the Issue – No Need to Change Law	52
(1) Safety of Food – “Food Can Be Dangerous”	52
(a) Peanuts – “Snickers”	52
VIII. CONCLUSION.....	55

I. Executive Summary

Ephedra containing dietary supplements (“Ephedra Supplements”) are safe and effective when used as directed pursuant to established industry standards. Placement of an explicit warning statement on the principal display panel (“PDP”) of these products along with strong uniform warnings on the outer packaging that will further enhance the safety of these products would be strongly supported by NVE Pharmaceuticals, Inc. of Newton, New Jersey (“NVE Pharmaceuticals”), a manufacturer and marketer of ephedra containing and other dietary supplements. Moreover, NVE Pharmaceuticals has committed to participating in a public education campaign to alert parents against the use of Ephedra Supplements by children under eighteen and to encourage the safe and responsible use of Ephedra Supplements by adults.

A recent report by the RAND Corporation (“RAND”), which was commissioned by the U.S. government to evaluate all available data on the safety and efficacy of Ephedra Supplements and ephedrine (the “RAND Report” or the “Report”), was widely anticipated by the Food and Drug Administration (“FDA” or the “Agency”) to be the authoritative voice on this subject.¹ The FDA publicly stated numerous times that it was awaiting the results of the RAND Report prior to taking any further position on the subject. On February 28, 2003, FDA released a new proposed warning for ephedra products and reopened the comment period for the 1997 proposed rule on dietary supplements containing ephedrine alkaloids. At the same time FDA released the RAND Report.

The RAND Report concluded that, based on available data, Ephedra Supplements are an efficacious treatment for moderate, short-term weight loss and that their use cannot be conclusively linked to serious adverse events, the occurrence of which was described as a

¹ Shekelle, P., Morton, S., Maglione M., et al., *Ephedra and Ephedrine for weight loss and Athletic Performance Enhancement: Clinical Efficacy and Side Effects*, Evidence Report/Technology Assessment No. 76 (Prepared by Southern California Evidence-based Practice Center, RAND, under Contract No. 290-97-0001, Task Order No. 9). AHRQ Publication No. 03-E022. Rockville, MD: Agency for Healthcare Research and Quality (February 2003) [hereinafter *The RAND Report*].

“rarity.” Furthermore, in evaluating case reports from FDA and from one of the largest manufacturers of Ephedra Supplements, RAND found insufficient information to make an informed judgment about the relationship between the use of Ephedra Supplements and the adverse events reported.

NVE Pharmaceuticals accepts the need for strong science based warnings on Ephedra Supplements and in that sense, supports much of what FDA has proposed in its most recent proposed regulation. In fact, the American Herbal Product Association (“AHPA”), of which NVE Pharmaceuticals is a member, has been one of the strongest proponents of warning language on Ephedra Supplements for many years, long before FDA issued its own proposed regulations.

The findings of the RAND Report do not support FDA’s position that a lengthy “black box” warning against the use of Ephedra Supplements is necessary. That portion of FDA’s proposal is misguided and unreasonable and represents a clear departure from current FDA regulations and policy on labeling. Indeed it appears that this position is not entirely science based, but is instead politically motivated. Moreover, NVE Pharmaceuticals cannot accept FDA’s suggestion that the Agency’s inability to remove ephedra from the marketplace in light of the RAND Report’s findings justifies a request for public comment in support of an effort to amend the Federal Food, Drug and Cosmetic Act (“FDCA” or “the Act”)² and roll back the Dietary Supplement Health and Education Act (“DSHEA”).³ FDA has vast enforcement powers under the law as it exists and those powers are unimpeded by DSHEA. FDA presently has the ability to take swift effective enforcement action against any dietary supplement that is adulterated and/or misbranded and can even initiate criminal proceedings for the sale of such

² Federal Food, Drug, and Cosmetic Act, 21 U.S.C. §§ 321 *et seq.*

³ Dietary Supplement Health and Education Act of 1994, Pub. L. No. 103-417 (1994).

products. No amendment to the law is necessary to allow FDA to undertake such actions in the interest of the public health.

NVE Pharmaceuticals, however, appreciates FDA's view that there is a need for clear and concise warning language to appear on the PDP of Ephedra Supplements. In light of this, NVE Pharmaceuticals suggests the adoption of the following PDP warning:

WARNING: Contains ephedrine alkaloids. Heart attack, stroke, seizure, and death have been reported after consumption of ephedrine alkaloids. Not for persons under 18. See more information on back panel.

FDA's current proposal fails to address a number of important concerns relating to the numerous state laws and regulations currently in place regarding ephedra. This complex framework raises concerns of consumer confusion and difficulties in compliance. NVE Pharmaceuticals therefore requests that FDA issue a statement indicating that the final ephedra warning regulation preempt state regulations.

According to U.S. Health and Human Services Secretary Tommy G. Thompson, overweight and obesity are among the most pressing new health challenges we face today.⁴ Obesity outranks both smoking and drinking in its deleterious effects on health and health costs.⁵ The responsible use of Ephedra Supplements, which RAND has concluded assists people in losing statistically significant amounts of weight (even if only for a short-term regimen), can provide a significant public health and cost benefit by addressing these issues.

II. What Is Ephedra?

A. *Ephedra Is an Herb*

Chinese Ephedra comes from dry herbaceous stems of a primitive family of plants known as Ephedraccac. Although there are over forty species of ephedra throughout Asia, Europe, the

⁴ HHS Secretary, Tommy G. Thompson, U.S. Food and Drug Administration, FDA Consumer magazine (March-April 2002).

⁵ Sturm, Roland, *The Effects of Obesity, Smoking, and Drinking on Medical Problems and Costs*, Health Affairs, (March/April 2002), p. 245. Roland Sturm is a senior economist at RAND.

Mediterranean, and North and South America, most commercial material comes from China because only those species contain ephedrine alkaloids.⁶ The species found in the Americas are alkaloid free and offer virtually no therapeutic value.⁷ Chinese *ephedra sinica* was introduced in the Dakotas in the 1930s and is believed to have spread and hybridized.⁸ It has been described by the U.S. Department of Agriculture as an excellent forage crop.

The term ephedra (or *ma huang* in Chinese) usually refers to one of three Chinese species: *Ephedra sinica* (most common), *Ephedra equisetina*, or *Ephedra intermedia*.⁹ All three are grown medicinally in China and are recognized in the Pharmacopoeia of the People's Republic of China as well as the Chinese Materia Medica. The beneficial properties of ephedra have been attributed to the alkaloid content found in the stems and leaves, which ranges from 0.5%-2.5%, depending on the species, time of harvest, weather conditions and altitude.¹⁰ Ephedrine was first isolated from *ma huang* in Japan in the late nineteenth century and started appearing in medical literature about 40 years later when K.C. Chen and C.F. Schmidt of the Peking College started publishing pharmacological studies on ephedrine.¹¹ Shortly thereafter, synthetic ephedrine was being used in the United States as a nasal decongestant, a central nervous system stimulant and for the treatment for bronchial asthma.¹²

Ephedrine and pseudoephedrine are the dominant alkaloids found in ephedra, with ephedrine making up 30-90% of the total alkaloid content.¹³ Other related alkaloids such N-methylephedrine, N-methylpseudoephedrine, norpseudoephedrine and norephedrine

⁶ Tyler VE, Brady LR, Robbers JE, *Pharmacognosy*, 9th Ed., Philadelphia: Lea & Febiger (1988); Morton J., *Major Medicinal Plants: Botany, Culture and Uses*, Springfield, IL: Charles C. Thomas, (1977).

⁷ *The Ephedras*, Lawrence Review of Herbal Natural Products (June 1989); Duke, (1985).

⁸ Christensen BV, Hinde LD, *Cultivation of Ephedra in South Dakota*. J. Am. Pharm. Assoc., 25, 969-973 (1936).

⁹ *Pharmacopoeia of the People's Republic of China*, English Edition (2000).

¹⁰ *The Ephedras*, *supra*, note 7; *Morton*, *supra* note 6.

¹¹ *Ma huang: Ancient Herb, Modern Medicine, Regulatory Dilemma; a Review of the Botany, Chemistry, Medicinal Uses, Safety Concerns, and Legal Status of Ephedra and its Alkaloids*, J. of Am. Botanical Council, Issue 34, p.22, (1995).

¹² Tyler VE, *Herbs of Choice: the Therapeutic Use of Phytomedicinals* (1994).

¹³ Chen KK, *A Pharmacognostic and Chemical Study of Ma Huang (Ephedra vulgaris var. Helvetica)*, J. Am. Pharm. Assoc., 14, 189-194 (1925); *The Ephedras*, *supra*, note 7.

(phenylpropanolamine) are also present. They have been collectively termed as “ephedrine group alkaloids.” Ephedra is usually sold as an extract, concentrated at about 6%-8% ephedrine alkaloids.

B. What Is Ephedrine?

Naturally occurring ephedrine alkaloids should not be confused with synthetic ephedrine, which is not derived from a botanical source and is not permitted for use in dietary supplements. FDA has specifically stated that synthetic ephedrine alkaloids are not “dietary ingredients” as defined by the FDCA and that products containing synthetic ephedrine alkaloids do not fall under the regulatory scheme of DSHEA. Synthetic ephedrine is currently used in many cold remedies and must be clearly identified on product labels as “ephedrine hydrochloride” or “ephedrine HCL.” It has been approved by FDA for use as a nasal decongestant and a bronchodilator in Over-The-Counter (“OTC”) drugs.¹⁴

There are significant differences between the effects of synthetic ephedrine and ephedra. This is because alkaloids are absorbed more slowly from the herb than from pharmaceutical formulations and because natural ephedra contains substances called ephedradines that cause blood pressure to fall and act to counter the effect of the ephedrine on the circulation.¹⁵ Although ephedradines are mainly found in the roots of the plant, it is believed that they are also found in the stems in small amounts.¹⁶ Therefore, while both synthetic ephedrine and ephedra produce similar effects, ephedra is considered much gentler and less likely to cause adverse effects such as palpitations.¹⁷ In one animal study, 689mg/kg (\cong 50g/human) of ephedrine was

¹⁴ Bronchodilator Active Ingredients, 21 C.F.R. §341.16; Nasal Decongestant Active Ingredients, 21 C.F.R. §341.20.

¹⁵ Reid DP, *Chinese Herbal Medicine*, 50, 81, Shambhala, Boston (1986); *Ma Huang: the Facts!*, Barriatrix Bulletin, (January 1995).

¹⁶ *Barriatrix Bulletin*, *supra* note 15.

¹⁷ Weiss, *Herbal Medicine*, Beaconsfield, England: Beaconsfield Publishers (1988).

required to kill 50% of the mice while the dose of alkaloids extracted from *ma huang* for the same effect was 5300mg/kg (\cong 370g/human).¹⁸

III. What Is Ephedra Used For?

Historically, ephedra products were commonly used for mild bronchospasms, bronchial asthma, nasal congestion, common colds, and sinusitis.¹⁹ Ephedra supplements have more recently become popular for weight loss and athletic performance. These new uses have been the subject of much debate and have gained national media attention.

A. History of Use

Ephedra has a long history of medicinal use documented in medical treatises from China and India. It has been called the oldest medicinal plant in continuous use. Use in Europe has been documented from the 15th to the 19th Centuries. *Ma huang* has been used for treating asthma, hay fever, hives, incontinence, narcolepsy, and myasthenia gravis (progressive weakness of voluntary muscles).²⁰ Ephedrine alkaloids were first used in western medicine as an asthma treatment in the 1930s.²¹ Since then, they have been used in many OTC products as decongestants and cold medicines.

1. Chinese Medicinal Purposes

In Asian medicine, the dried stems of the ephedra plant known as *ma huang* have been the primary herbal treatment for asthma and bronchitis. It has been used in Traditional Chinese Medicine for over 5,000 years for the treatment of colds, flu, fever, chills, headache, edema, bronchial asthma, lack of perspiration, nasal congestion, aching joints and bones, and coughs and

¹⁸ Minamitsu et al., *Acute Ephedrae Herba and Ephedrine Poisoning in Mice*, Japan. J. of Toxicology, 4, 143-149 (1991).

¹⁹ Blumenthal M., Busse WR, Goldberg A., Gruenwald J., Hall T., Riggins CW, Rister RS (eds.), Klein S., Rister RS (trans.), *The Complete German Commission E Monographs – Therapeutic Guide to Herbal Medicine*, Austin, TX: American Botanical Council; Boston Integrative Medicine Communication, (1998); World Health Organization (WHO), *Herba Ephedrae in: WHO Monographs on Selected Medicinal Plants*, Vol. 1, Geneva: World Health Organization, (1999):145-53.

²⁰ BHP, (1983); WHO, *supra* note 19; Blumenthal, *supra* note 19.

²¹ U.S. Pharmacopoeia, Revision no. 11 (1936).

wheezing.²² The roots were also used in the treatment of spontaneous and night sweating and as an anti-allergy agent. Ephedra is listed in the oldest comprehensive material medica, *Shen Nong Ben Cao Jing*.²³

2. History of Use in Weight Loss

It was not until the 1970s that the weight loss properties of ephedrine were discovered. In 1972, a Danish doctor treating asthma patients with ephedrine, caffeine, and phenobarbital noticed unintentional weight loss.²⁴ The results attracted the attention of obesity researchers who later showed that the combination of ephedrine and caffeine, even at low dosages, could double the rate of weight loss compared to a placebo.²⁵ Ephedra, with and without caffeine, has been marketed in the United States as a weight loss aid since the early 1990s.

B. Extent of Use

Ephedra is used extensively in the United States for a variety of purposes. According to a survey of fourteen (14) ephedra manufacturers conducted by AHPA in 1999, 425 million ephedra “servings” were sold in 1995, rising to 3 billion servings in 1999, for a total estimate of 6.8 billion ephedra servings sold.²⁶ Currently, between 12 and 17 million Americans consume more than three billion servings of Ephedra products every year.²⁷

²² Ou Ming, *Chinese-English Manual of Common-Used Herbs in Traditional Chinese Medicine*, Guangdong Science & Technology Publishing House and Joint Publishing Co., Hong Kong, 492-493 (1989); Leung A., Foster S., *Encyclopedia of Common Natural Ingredients Used in Food, Drugs and Cosmetics*, 2nd Ed., New York, NY, John Wiley & Sons, Inc. (1996).

²³ Blumenthal M., King P., *The Agony of the Ecstasy: Herbal High Products get Media Attention*, (1995); Bruneton, J. *Pharmacognosy, Phytochemistry, Medicinal Plants*, Paris, France: Lavoisier Publishing, 1995:711-4.

²⁴ Malchow-Moller et al., *Ephedrine as an Anorectic: the Story of the ‘Elsinore Pill,’* *Int. J. Obes.*, 5, 183-187 (1981).

²⁵ Toubro S., Astrup A., Breum L., Quaade F., *Safety and Efficacy of Long-term Treatment with Ephedrine, Caffeine and an Ephedrine/Caffeine Mixture*, *Int. J. Obesity*, 17, S69-S72 (1993); Daly PA, Krieger DR, Dullo AG, et al, *Ephedrine, Caffeine, and Aspirin: Safety and Efficacy for Treatment of Human Obesity*, *Int. J. Obes.*, 17 (suppl):S73-8 (1993).

²⁶ Despite a 700% increase in sales between 1995 and 1999, only 66 serious adverse events were reported by the companies surveyed. This represents a reporting rate of less than 10 adverse events per billion serving sold. AHPA defines “serious adverse event” as any report of a person suffering a heart attack, stroke, seizure, death or other injury that resulted in hospitalization or treatment by a physician. McGuffin M., Statement Before the Department of Health and Human Services Office of Public Health & Sciences, Public Meeting on Safety of Dietary Supplements Containing Ephedrine Alkaloids (Aug. 2000).

²⁷ McGuffin, (2000), *supra* note 26.

Currently, ephedra is listed in the national pharmacopoeias of China, Germany and Japan.²⁸ Japan requires no less than 0.6% total alkaloids.²⁹ China requires at least 0.8% and Germany 1%.³⁰ Isolated ephedrine alkaloids (i.e. ephedrine; pseudoephedrine) are also listed in most countries.

IV. FDA's Regulation of Ephedra (Prior and Current Issues)

A. FDCA / DSHEA

Ephedra Supplements are legally marketed as dietary supplements under the FDCA and have been so since the passage of DSHEA in 1994.³¹ A dietary supplement is defined as a product (other than tobacco) that is 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 daily intake, or a concentrate, metabolite, constituent, extract, or combinations of these ingredients.³² Dietary supplements, which are required to be labeled as such,³³ must be intended

²⁸ A book containing an official list of medicinal drugs together with articles on their preparation and use.

²⁹ *Japanese Pharmacopoeia*, (1993).

³⁰ *Pharmacopoeia of the People's Republic of China*, (1997); *German Pharmacopoeia*, (1999).

³¹ FDA traditionally considered dietary supplements to be composed only of essential nutrients, such as vitamins, minerals, and proteins. The Nutrition Labeling and Education Act of 1990 added "herbs, or similar nutritional substances," to the term "dietary supplement." Pub. L. No. 101-535, 104 Stat. 2353 (1990). Through the DSHEA, Congress expanded the meaning of the term "dietary supplements" beyond essential nutrients to include such substances as ginseng, garlic, fish oils, psyllium, enzymes, glandulars, and mixtures of these.

³² See 21 U.S.C. § 321(ff)(1)(A)-(F). The definition of a dietary supplement also includes products such as an approved new drug, certified antibiotic, or licensed biologic that was marketed as a dietary supplement or food before approval, certification, or license (unless the Secretary of Health and Human Services waives this provision). The genesis of the provision in the law allowing the combination of herbal ingredients in a supplement has its roots in the black current seed oil cases where the 1st and 7th Circuit Court of Appeals held that FDA's position that black current seed oil sold alone was legal but once inserted into a capsule was converted into an unapproved food additive, "defenestrates common sense."

³³ See 21 U.S.C. § 321(ff)(2)(C).

for ingestion in pill, capsule, tablet, or liquid form,³⁴ and they must not be represented for use as a conventional food or as the sole item of a meal or diet.³⁵

Under the FDCA, Ephedra Supplements are subject to FDA's general regulatory authority and are subject to seizure, condemnation or destruction if they are determined to be "adulterated"³⁶ and/or "misbranded"³⁷ or if the product or an ingredient contained therein poses an "imminent hazard" to public health or safety.³⁸ The passage of DSHEA actually expanded FDA's regulatory authority to stop the distribution of unsafe dietary supplements. Under DSHEA, a dietary supplement is considered adulterated if it 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 or recommended in the labeling, under ordinary conditions of use.³⁹ DSHEA was also responsible for the addition of the "imminent hazard" provision.

B. 1997 Proposed Warnings and Formulation Changes ("1997 Proposed Rule")

In June 1997, the FDA proposed severe limits on the manufacture and use of ephedra that would have rendered ephedra products useless for their intended purposes.⁴⁰ Based on Adverse Event Reports ("AERs") solicited by the agency between 1993 and 1997, FDA proposed to:

- Limit product potency to less than 8mg ephedrine alkaloids per serving.
- Restrict daily dosages (24mg).
- Require labels to contain the following statement: "Do not use this product for more than 7 days."

³⁴ See 21 U.S.C. § 350(c)(1)(B)(i). The definition of a dietary supplement also includes products such as an approved new drug, certified antibiotic, or licensed biologic that was marketed as a dietary supplement or food before approval, certification, or license (unless the Secretary of Health and Human Services waives this provision).

³⁵ See 21 U.S.C. § 321(ff)(2)(B). The definition of a dietary supplement also includes products such as an approved new drug, certified antibiotic, or licensed biologic that was marketed as a dietary supplement or food before approval, certification, or license (unless the Secretary of Health and Human Services waives this provision).

³⁶ See 21 U.S.C. § 342.

³⁷ See 21 U.S.C. § 343.

³⁸ See 21 U.S.C. § 342(f)(1)(C). Only the Secretary declares a dietary supplement or dietary ingredient an imminent hazard to public health or safety. The authority to make such declaration shall not be delegated and the Secretary shall promptly after such a declaration initiate a proceeding in accordance with §§ 554 and 556 of title 5, U.S.C. to affirm or withdraw the declaration.

³⁹ See 21 U.S.C. § 342(f)(1)(A).

⁴⁰ See 62 Fed. Reg. 30678.

- Prohibit the combination of *ma huang* with other stimulants such as caffeine.
- Prohibit certain labeling claims that encourage long-term use (e.g. weight loss; bodybuilding).
- Require a warning for claims that encourage excessive short-term intake ("Taking more than the recommended serving may result in heart attack, stroke, seizure or death").

FDA's proposed rule was highly controversial and prompted numerous responses from other government agencies as well as industry organizations and consumers.

1. Government Responses to FDA Proposed Rules

a) U.S. Small Business Administration (SBA) - Office of Advocacy; Comments

In response to the proposed rule, the SBA Office of Advocacy filed extensive comments expressing the concerns of small businesses and questioning FDA's cost-benefit analysis of the proposal. The SBA comments also addressed the apparent lack of scientific evidence supporting the proposed restrictions, and the fact that FDA never established a baseline for its scientific analysis.⁴¹ The SBA comments were so persuasive that they were instrumental in activating congressional involvement with the ephedra proposal.

b) U.S. General Accounting Office ("GAO Report")

Following the SBA comments, the House Committee on Science requested that the Government Accounting Office (GAO) conduct an audit of FDA's scientific basis for the proposed restrictions on ephedra products and asked the GAO to examine FDA's cost/benefit analysis justifying the need for a regulation.

In 1999, the GAO confirmed in an 80-page report that FDA did not have a sufficient scientific basis for the proposed serving and duration limits and that the Agency's cost/benefit analysis was deficient in many respects.⁴² The GAO reported that FDA's conclusions were

⁴¹ Letter from Jeff W. Glover, Chief Counsel for Advocacy, SBA Office of Advocacy, to the Department of Health and Human Services, FDA (Feb 3, 1998).

⁴² Report to the Chairman and Ranking Minority Member, Committee on Science, House of Representatives, *Dietary Supplements: Uncertainties in Analyses Underlying FDA's Proposed Rule on Ephedrine Alkaloids* (July 1999). (The "GAO Report").

“open to question because of limitations and uncertainties associated with the agency’s underlying scientific evidence and economic analysis.” GAO found no evidence to support the recommended dosage levels (i.e. 8 mg/serving and 24 mg/daily) and duration limits (7 days) of ephedra in its proposed regulation. GAO pointed to the inherent weakness of the AERs as well as FDA’s heavy reliance on them. Out of the 800 AERs submitted to the agency, FDA based its proposed dosage limits on only 13 reports. Furthermore, FDA did not perform any causal analysis to determine if the reported events were, in fact, caused by the ingestion of dietary supplements containing ephedrine alkaloids.

2. FDA Withdraws Much of the Proposed Regulation

As a result of increased criticism by policy-makers and the general public, as well as the GAO Report that the Agency lacked a sound scientific basis for its proposal, on April 3, 2000, FDA withdrew the proposed restrictions concerning potency, labeling claims, and directions for use on ephedra products.⁴³ Despite the findings of the GAO Report and FDA’s withdrawal, the Agency appeared to maintain the position that the reported adverse events justify the need for a new regulatory scheme for ephedra products. FDA interpreted the GAO’s finding that the Agency lacked scientific evidence to support its proposed dosing level and duration of use limit restrictions as a need for its reassessment of the proposal, but at the same time, a justification. In its withdrawal, FDA highlighted the GAO’s conclusion that “FDA was justified in determining that the number of adverse event reports relating to dietary supplements containing ephedrine alkaloids warranted the agency’s attention and consideration of steps to address safety issues.”⁴⁴ In fact, at the same time FDA withdrew the proposed restrictions, it released 140 additional

⁴³ See 65 Fed. Reg. 17474.

⁴⁴ See *Id.* at 17475.

AERs “associated with dietary supplement products that were known or suspected to contain ephedrine alkaloids.”⁴⁵

3. U.S. Department of Health and Human Services Public Meeting on Ephedra Safety (August 2000)⁴⁶

In response to the 1999 GAO Report and FDA’s withdrawal of the substantive portions of its proposed rule, the Department of Health and Human Services (“HHS”) Office on Women's Health (OWH) sponsored a public meeting to discuss the safety of dietary supplements containing ephedrine alkaloids (“Ephedra Hearing”). At the meeting, FDA and its consultants maintained their previously unsupportable positions from the 1997 proposal that dietary supplements containing ephedrine alkaloids are associated with serious adverse health effects. However, independent researchers and leading academic experts were given the opportunity to rebut FDA’s position by showing that FDA’s AERs were not useful scientific evidence,⁴⁷ that FDA had ignored data from experts in the field of obesity indicating the benefits of ephedra,⁴⁸ and that FDA had completely mischaracterized the scientific literature on these products.⁴⁹ Also, a panel presented on behalf of the Ephedra Education Council (EEC) presented consensus findings on the safety of dietary supplements containing ephedrine alkaloids.⁵⁰

⁴⁵ 65 Fed. Reg. 17510.

⁴⁶ Department of Health and Human Services, Office on Women’s Health, Public Meeting on the Safety of Dietary Supplements Containing Ephedrine Alkaloids (Aug 8, 2000) [hereinafter *Ephedra Hearing*].

⁴⁷ Dr. Grover M. Hutchins, a leading researcher in pathology and cardiac pathology and a Professor of pathology at the Johns Hopkins University School of Medicine, reported that after reviewing all 22 deaths reported to FDA which the agency included as “possibly related” to the consumption of ephedrine alkaloids, there was no indication that ephedrine alkaloids were a contributing factor or a causative factor in the deaths.

⁴⁸ A panel of leading obesity experts, including Dr. George Bray, Dr. Arne Astrup, and Dr. Gary Huber, testified to the effectiveness of dietary supplements containing ephedrine alkaloids for weight loss.

⁴⁹ Dr. Steven Karch, an expert in cardiac pathology and cardio toxicity and Assistant Medical Examiner of the City and County of San Francisco, presented a point-by-point rebuttal of FDA’s literature review showing that FDA misrepresented the scientific literature and relied on inappropriate studies.

⁵⁰ See V(A)(1) Ephedra Education Council (EEC) Expert Panel Report, *infra*.

C. 2003 Proposed Rule

On February 28, 2003, FDA reopened the comment period for the 1997 proposed rule on dietary supplements containing ephedrine.⁵¹ FDA announced that it is seeking rapid public comments on 1) new evidence of health risks associated with ephedra including the much anticipated RAND Report.⁵² 2) whether ephedra presents “a significant or unreasonable risk of illness or injury,” and 3) a new proposed warning for ephedra products. In addition, FDA issued nearly thirty warning letters against ephedra products making allegedly unsubstantiated claims about sports performance enhancement. FDA also solicited public support for its position that public safety requires amendment of DSHEA.

1. New Warning

Under FDA’s current proposed rule, the following warning statement would appear on the principal display panel (front panel) of all ephedra products:

WARNING: Contains ephedrine alkaloids. Heart attack, stroke, seizure, and death have been reported after consumption of ephedrine alkaloids. Not for pregnant or breast-feeding women or persons under 18. Risk of injury can increase with dose or if used during strenuous exercise or with other products containing stimulants (including caffeine). Do not use with certain medications or if you have certain health conditions. Stop use and contact a doctor if side effects occur. See more information [...].

The information below (the “back panel warning”) would also need to appear on the outer product label or in product labeling so that it can be read at the point of purchase.

⁵¹ See 68 Fed. Reg. 10417, (Docket No. 95N-0304).

⁵² Bent, *The Relative Safety of Ephedra Compared with Other Herbal Products*; Morgenstern, *Use of Ephedra-containing Products and Risk of Hemorrhagic Stroke*; Samenuk *Adverse Cardiovascular Events Temporally Associated with ma huang, an Herbal Source of Ephedrine*; Haller, *Pharmacology of Ephedra Alkaloids and Caffeine After Single-dose Dietary Supplement Use*; Boozer, *Herbal Ephedra/Caffeine for Weight Loss: a 6-month Randomized Safety and Efficacy Trial*; *The RAND Report*.

This product contains ephedrine alkaloids, which can have potentially dangerous effects on the heart and central nervous system.

Do not use with

- ✓ a monoamine oxidase inhibitor (MAOI) or for 2 weeks after stopping a MAOI drug;
- ✓ certain drugs for depression, psychiatric, or emotional conditions;
- ✓ drugs for Parkinson's disease;
- ✓ drugs for obesity or weight control;
- ✓ methyldopa.

Contact a doctor before using this product if you have or ever had

- ✓ heart disease, high blood pressure, thyroid disease, seizure, diabetes, depression, other mental, emotional or behavioral conditions, glaucoma, or difficulty urinating due to prostate enlargement.

Stop use and contact a doctor immediately if these side-effects occur

- ✓ dizziness, severe headache, rapid and/or irregular heartbeat, chest pain, shortness of breath, nausea, loss of consciousness, or changes in emotions or behavior (such as depression, hallucinations or severe mood swings).

Your risks of serious side-effects from this product can increase

- ✓ with increased dose, frequency, or duration of use;
- ✓ if you take it with other dietary supplements containing ephedrine alkaloids (such as ephedra, ma huang, *Sida cordifolia*);
- ✓ if you take it with additional products containing stimulants, such as caffeinated beverages and foods (including dietary supplements containing guarana, kola nut, mate, yohimbine/yohimbe, *Citrus aurantium*);
- ✓ if you take it with medications containing synephrine, phenylephrine, ephedrine, pseudoephedrine, or phenylpropanolamine;
- ✓ if you use it before or during strenuous exercise.

2. No Formulation Issues Named

Unlike the 1997 proposal, there are no proposed restrictions on the formulation of ephedra dietary supplements. However, the new proposed warning does indicate on the front panel that “risk of injury can increase with dose” and on the other panel that “serious side-effects from this product can increase with increased dose, frequency, or duration of use.” FDA also appears to have abandoned its proposed prohibition on dietary supplements that combine ephedrine alkaloids with other stimulants such as caffeine. However, under the current proposal, both warning panels would indicate that the risk of injury or serious side effects can increase if ephedra is used with other products containing stimulants such as caffeine.

3. No Preemption Issue Is Addressed

Even though FDA has the authority to determine which rules, regulations, or other administrative actions will have pre-emptive effect, FDA's proposal does not include a provision expressly preempting state law regulating Ephedra Supplements.⁵³ Without federal preemption, there cannot be national uniformity. Compliance by Ephedra Supplement manufacturers and marketers will be unduly complicated as well as extremely costly, as a number of states have already adopted different requirements with regard to Ephedra Supplements. Ephedra Supplements will inevitably bear inconsistent warning statements from product to product and from state to state. Additionally, consumers will be unduly confused to their detriment by this lack of uniformity. Including an express preemption clause in the final rule is the most effective way to ensure nationally uniformity, which appears, on its face, to be FDA's intent.

a) State and Local Regulation of Ephedra

Due to the long absence of a clear federal policy on Ephedra Supplements, a number of states have established their own requirements, either by legislative action or through a regulatory process. Several states require lengthy label warnings on Ephedra Supplements (*e.g.*, California,⁵⁴ Texas,⁵⁵ Nebraska,⁵⁶ and Idaho⁵⁷) – and in many cases the warning label required by one state differs from that required by another. Other states require limited warning statements on Ephedra Supplements (*e.g.*, Ohio⁵⁸ and Michigan⁵⁹). Many states require label statements regarding the amount of ephedrine alkaloids and other stimulants in the Ephedra

⁵³ The Supreme Court has suggested that, in the absence of a clear congressional command as to pre-emption, courts may infer that the relevant administrative agency possesses a degree of leeway to determine which rules, regulations, or other administrative actions will have pre-emptive effect. See *Medtronic v. Lohr*, 518 U.S. 470 (1996), citing *Hillsborough County v. Automated Medical Laboratories, Inc.*, 471 U.S. 707, 721 (1985) (Breyer, J., Concurring) (Congress' intent may be found in federal regulations that are duly enacted pursuant to delegation of congressional authority).

⁵⁴ Cal. Health & Safety Code § 110423 (a) (1), (2), Section 110423 (c).

⁵⁵ 25 Tex. Admin. Code 229.462.

⁵⁶ Neb. Rev. Stat. § 28-448.

⁵⁷ IDAPA 27.01.01.158 02.c.

⁵⁸ Ohio Rev. Code § 3719.44, Div. (K)(2)(a).

⁵⁹ Mich. Admin. Code § 333.7220 (c)(ii).

Supplement and many require a label statement regarding the maximum recommended individual (25mg) and daily (100mg) dosage and duration of use (12 weeks). Some states even require the FDA disclaimer,⁶⁰ even if there are no structure/function statements on the product label (e.g., Nebraska⁶¹ and Idaho⁶²). Texas requires a separate warning on all promotional materials.⁶³ A number of states prohibit sales to persons less than 18 years of age⁶⁴ or require that products be kept behind the counter in retail settings.⁶⁵

4. FDA Rhetoric Unfounded

The current proposed rule was announced with much fanfare by FDA at 3 pm on Friday, February 28, 2003. At that time, the Agency also issued a press release, a white paper on Ephedra, a list of warning letters issued including a sample of the same and the full text of the RAND Report (along with a summary), which supposedly constituted the scientific basis for the proposed regulation. Instead of fairly and responsibly reporting the findings of the RAND Report, FDA chose to perpetuate its mischaracterization of the “dangers” associated with the use of ephedra, and attempted to suppress the fact that ephedra could prove to be a significant health benefit when used responsibly.

a) Media Distortion of the Safety of Ephedra

The media has played a large part in perpetuating the myth that ephedra is unreasonably dangerous. They often refer to ephedra products (and dietary supplements in general) as being unregulated, which is wholly inaccurate.⁶⁶ Furthermore, they associate Ephedra Supplements with serious adverse events such as heart attack, stroke and death, when these events have never

⁶⁰ Under DSHEA, FDA requires that every product that bears a statement regarding the structure or function of the human body, must use include on its labeling (on the same panel where the claim is made) a bolded disclaimer surrounded by a hairline box. The disclaimer must read as follows: “This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure or prevent any disease.”

⁶¹ Neb. Rev. Stat. § 28-405.

⁶² IDAPA 27.01.01.158 02.c.v.

⁶³ 25 Tex. Admin. Code 229.462(g).

⁶⁴ e.g. Texas & California.

⁶⁵ e.g. St. Charles County, Missouri.

⁶⁶ See V(A)(6)(b) Regulatory Status Distorted by Media, *infra*.

be conclusively linked with the use of ephedra, even by the highly anticipated RAND Report. Where does the media get this inaccurate information? One source is FDA itself, which has repeatedly misrepresented scientific data.

(1) Recent Adverse Event in the News

(a) Steve Bechler

The cause of death of Baltimore Orioles pitcher, Steve Bechler, on February 16, 2003, was immediately reported by the media to be due to the ephedra supplement Xenadrine RFA-1, long before the Broward County medical examiner, Dr. Joshua Perper, had even concluded his examination of the body. While it is true that final toxicology tests released in March 2003 "revealed significant amounts of ephedrine" in Bechler's blood along with low amounts of two other ephedrine alkaloids (pseudoephedrine and caffeine), Dr. Perper's report also indicated that Bechler "had a constellation of risk factors that acted in unison and prompted" his death. These factors include "being significantly overweight and not well conditioned," "not yet being acclimatized to the warm climate of Florida," and "having hypertension and abnormal liver function."⁶⁷ The amount of ephedrine found in his blood was "consistent with [Bechler] taking three or more tablets of the weight-loss supplement Xenadrine [RFA-1]" as was earlier reported by his teammates.⁶⁸ The recommended dose is two tablets per day.

The fact that the Ephedra Supplement may have been a contributing factor in Mr. Belcher's death cannot alone determine that Xenadrine, or ephedra in general is unsafe. In the case of Mr. Belcher, who suffered from liver disease and who was being treated for hypertension, he took the product against the explicit instructions and warnings on the Xenadrine label, which specifically states: "Do not use if you are at risk or being treated for high blood

⁶⁷ Tan Sheets (March 17, 2003).

⁶⁸ Sports Illustrated (Internet Site), *Ephedra a factor - Coroner finds 'significant amounts' of diet supplement* (March 13, 2003).

pressure, liver, ...disease.” This information was left out of many of the news reports that followed Mr. Bechler’s death, and has never been acknowledged by any FDA official.

The circumstances surrounding Bechler’s death, while tragic, would not be very different from those of a person with a known allergy to peanuts experiencing an adverse event after eating a Snicker’s Bar, knowing that the candy contains peanuts after reading the label. The person consuming the product is responsible for reading such labels and for following the instructions. NVE Pharmaceuticals fully supports the use of strong warning language to ensure products are used safely and has already taken steps to ensure that consumers understand both FDA’s concerns and the circumstances for safe, responsible use of ephedra.

(b) Korey Stringer

The cause of death of Minnesota Viking Korey Stringer in 2001 has been identified as heatstroke, but ask anyone who has been keeping up with recent news on ephedra and they may tell you otherwise. Since Mr. Bechler’s death, the media has given renewed attention to the untimely death of Mr. Stringer, who the Vikings allege was using an ephedra product called Ripped Fuel at the time. Mr. Stringer’s wife has filed a wrongful death lawsuit against the Vikings claiming that Vikings’ doctors and trainers were negligent when caring for her husband who died of heatstroke after collapsing at training camp. She also claims that toxicology results failed to show the presence of ephedrine.⁶⁹

(c) Anne Marie Capati

The 1998 death of a woman in a New York City gym after taking an ephedra product recommended by her personal trainer, which was widely reported at the time, has also recently received renewed media attention. Her death, which was apparently caused by the interaction between the ephedra and her high blood pressure (or her high blood pressure medication), was

⁶⁹ Sports Illustrated (Internet Site), “*Causally linked*” - Vikings: Stringer’s use of ephedra contributed to death (February 25, 2003).

more likely related to the negligence of her personal trainer than to the product itself. It has been reported that the trainer told her to take the ephedra supplement for weight loss even though he knew she was taking medication for high blood pressure.⁷⁰

D. The RAND Report

1. Introduction

The RAND Report was commissioned by the National Institute of Health to review evidence on the risks and benefits of ephedra and ephedrine. It was prepared for the U.S. Department of Health and Human Services and was released by FDA on February 28, 2003.

A review of The RAND Report indicates that parts of FDA's proposed regulation may not be supported by the scientific evidence contained therein, while FDA's rhetoric certainly is not. Nevertheless, NVE Pharmaceuticals continues to support the use of strong warning language on Ephedra Supplements. In fact, warning language similar to FDA's proposed back panel warning has been a part of the natural product industry's voluntary standards for years.

2. Common Terminology Used in Clinical Studies vs. RAND Terminology

To best understand the RAND Report, it is important to understand the terminology commonly used in clinical studies and case reports [although some case reporting systems, especially those created in private industry, may utilize their own terminology]. In contrast, it is equally important to know the meaning of the language used by RAND in its Report as it can be confusing.

a) Adverse Events vs. Side Effects

The terms "adverse event"⁷¹ and "side effect"⁷² are generally used imprecisely and interchangeably. Scientifically, however, the attributes, which together contribute to the safety

⁷⁰ Katherine Hobson, *Danger at the gym*, U.S. News and World Report, p 59 (January 21, 2002).

⁷¹ See Define Adverse Event, *infra*.

⁷² See Define Side Effect, *infra*.

(or lack of safety) of a substance that is ingested by humans, are distinct, and any safety evaluation of the substance must allow for this distinction.

b) Define Expected Event

It is equally as important to fully understand the scope of the effects that are intended, as well as expected and desired, by a consumer from the consumption of a particular product as these effects are not “adverse events” or even “side effects.” These effects are generally indicated on the product label.

(1) Expected Events of Ephedra Supplements

(a) Weight Loss – Loss of Appetite

Weight loss is an expected event from taking Ephedra Supplements when they are sold for that purpose. It would therefore be fair to state that a consumer report describing a “loss of appetite” should not be classified as an “adverse event” or a “side effect,” as this effect is intended and fully expected.⁷³

(b) Energy

Increased energy is also an expected event from ephedra consumption because ephedra is a stimulant (like caffeine), and it is often sold for just that purpose. If a consumer takes the Ephedra Supplement for its stimulating effects, a complaint of sleeplessness or similar effect should not be characterized as a “side effect” or “adverse event” because such effect is intended and fully expected.⁷⁴

(c) Combination Products

Many Ephedra Supplements contain both ephedrine alkaloids and caffeine. It should be expected that these products will, depending on dose, help restore mental alertness or

⁷³ Research suggests that ephedrine and ephedra with caffeine reduces food intake (appetite).

⁷⁴ If a person takes an Ephedra Supplement for its weight loss effects, a complaint of sleeplessness may be more appropriately described as a “side effect.” It should never be described as an “adverse event.”

wakefulness when experiencing fatigue or drowsiness (sleeplessness) and possibly diminish appetite.

c) Define Side Effect

A side effect is an extension of the expected actions of a product (an agent) which is unwanted within the context of use of that product (agent), is dose-dependant and is reversible on cessation of use of the product (agent) or on reduction of dosage, without direct temporary or permanent damage to physical structures or metabolic systems. Second, a side effect is an action of the product (agent), which is attributable to its known mode of action, but unanticipated at the dose level used. A side effect is simply an extension of pharmacological activity.⁷⁵

(1) Known Side Effects from Ephedra

Like other stimulants such as coffee, ephedra can have side effects. Ephedra contains ephedrine alkaloids, which are pharmacologically active. These effects are to be expected for some consumers, especially when the product is not used as directed. As such, they should be clearly indicated on product labels, whether or not they are obvious to the consumer.

Furthermore, adults should be expected to take Ephedra Supplements just as responsibly as OTC and prescription drugs, other supplements and foods. If a consumer believes that he/she is more susceptible to stimulants like caffeine or ephedra, he/she is responsible for watching his/her own dosage accordingly. If a consumer, however, misuses or overuses any product, including Ephedra Supplements, they might experience the side effects known for that product. Some side effects of ephedra usage are nervousness, dizziness, tremors, alteration in heart rate, gastrointestinal distress, or chest pain.

(2) Known Side Effects from Caffeine

Caffeine is another stimulant that may cause side effects and is consumed precisely for its stimulating effect on the body. The OTC monograph for caffeine pills therefore requires the

⁷⁵ Jones, D., *Safety of Ephedra Herb, A Preliminary Report* (1995).

following label warning: “The recommended dose of this product contains about as much caffeine as a cup of coffee. Limit the use of caffeine-containing medications, foods, or beverages while taking this product because too much caffeine may cause nervousness, irritability, sleeplessness, and, occasionally, rapid heart beat.”⁷⁶ It is important to note that many Ephedra Supplements also contain caffeine.⁷⁷

d) Define Adverse Event

An adverse event is an effect of a product (agent), whether perceived by the user or not, that results in direct damage to a physical structure or metabolic system, that is more than a transient duration, usually long-lasting or permanent.⁷⁸ Examples of adverse events include myocardial infarction, hepatitis, stroke, seizures, psychosis, and even death.⁷⁹

e) Different Terminology Used by RAND

The RAND Report used markedly different terminology to refer to specific events that may or may not be associated with usage of Ephedra Supplements. RAND uses the terms “Adverse Event,” “Serious Adverse Event,” “Sentinel Event,” “Possible Sentinel Event,” and “Probably Not Related.”

(1) “Adverse Event”

Examples of “Adverse Events” (not necessarily associated with Ephedra Supplements) as described by RAND include the following: psychiatric symptoms (euphoria, neurotic behavior, agitation, irritability, anxiety, giddiness, etc), autonomic hyperactivity (tremor, twitching, jitteriness, insomnia, sweating, , etc.), nausea/vomiting (vomiting, upset stomach, heartburn, etc), palpitations (palpitations, irregular heartbeat, pounding heartbeat, etc.), tachycardia (elevated heart rate, tachycardia), hypertension (increase systolic or diastolic blood pressure) and

⁷⁶ 21 C.F.R. § 340.50(c)(1)

⁷⁷ RAND was unable to accurately determine in many circumstances whether the reported side effects from persons taking Ephedra Supplements were from the ephedra or from the caffeine.

⁷⁸ Jones, D., *supra* note 75.

⁷⁹ RAND characterizes these events as a “rarity.” See No Support that Ephedra is an Unreasonable Risk., *supra*.

headache.⁸⁰ These “adverse events,” as described by RAND, are similar to some of the “side effects” discussed above.

(2) “*Serious Adverse Event*”

Examples of “Serious Adverse Events” as described by RAND include death, myocardial infarctions, strokes, seizures, and serious psychiatric symptoms.⁸¹ These “serious adverse events” are similar to the “adverse events” discussed above.

(3) “*Sentinel Event*”

RAND determined that it could not reliably assign assessments of causality to case reports. Rather, RAND tried to identify those cases that would be classified medically as “idiopathic” in etiology, meaning the cause is not known. For such cases, given the known pharmacology of ephedrine, if use of ephedra or ephedrine was documented, a potential role for ephedra or ephedrine in causing the event must be considered. RAND classified such cases as “sentinel events.”

In order to be classified as a sentinel event, three criteria had to be met:⁸²

1. Documentation existed that an adverse event meeting RAND’s selection criteria occurred.
2. Documentation existed that the person having the adverse event took an ephedra-containing supplement within 24 hours prior to the event (only for cases of death, myocardial infarction, stroke, or seizure).
3. Alternative explanations were investigated and excluded with reasonable certainty.

⁸⁰ *The RAND Report*, pp 86-87; It should be noted that the RAND Report did not find a statistically significant association between the usage of ephedra supplements and alteration of blood pressure or headache(s).

⁸¹ *The RAND Report*, p. 25.

⁸² *The RAND Report* p. 30.

(4) “Possible Sentinel Event”

Cases where another condition by itself could have caused the adverse event, but for which the known pharmacology of ephedrine made it possible that ephedra or ephedrine may have helped precipitate the event, were classified as “possible sentinel events.”⁸³

(5) “Probably Not Related”

“Probably not related” was used for events that had other clear causes discovered on detailed investigation and to which the pharmacology of ephedrine was unlikely to have potentially contributed.⁸⁴

3. Findings

a) Efficacy Findings in Weight Loss

The studies analyzed by RAND indicated a weight loss of approximately 2 pounds per month greater than that of placebo.⁸⁵ These numbers equal a range of weight reduction between 5 and 11 percent of a patients’ pre-treatment weight.

(1) What Data Did RAND Analyze?

A total of 46 controlled clinical studies were found assessing weight loss, from both a comprehensive literature review and from the solicitation of unpublished studies. However, since RAND only accepted studies of weight loss that were controlled trials of human subjects with treatment periods of at least eight weeks, 20 of the 46 studies were excluded from RAND’s analysis and six more were excluded for a variety of other alleged reasons.

Accordingly, the RAND Report evaluated for efficacy a total of twenty (20) clinical trials that assessed 678 persons who consumed ephedra or ephedrine over a period of up to six

⁸³ *The RAND Report*, p. 31.

⁸⁴ *Id.*

⁸⁵ 1.8 pounds per month for ephedra alone, 2.1 pounds per month for ephedra with caffeine and 2.2 pounds per month for ephedrine.

months.⁸⁶ The Report analyzed five (5) trials on the effects of ephedrine versus placebo,⁸⁷ twelve (12) trials on ephedrine plus caffeine versus placebo,⁸⁸ three (3) trials on ephedrine plus caffeine versus ephedrine alone,⁸⁹ one (1) trial on ephedra versus placebo,⁹⁰ and four (4) trials assessing ephedra plus herbs containing caffeine versus placebo.⁹¹

⁸⁶ Data from 20 trials was used to determine efficacy of Ephedra Supplements, however, in an effort to present the data in the most organized and coherent fashion, RAND categorized these 20 trials into six different categories, some of which overlapped.

⁸⁷ Jensen KB, Dano P., Draeby N., Hansen SH, Kanstrup J. *Elsinore Tablets and Ephedrine as Slimming Agents*, Ugeskr Laeger, 142(23):1499-501; 411 (1980); Lumholtz IB, Thorsteinnsson B, Wamberg T, Lehnschau A, Hansen G, Spellerberg S, et al., *Ephedrine in the Treatment of Obesity. A Double-blind Cross-over Trial of the Effect of Elsinore Tablets*. Ugeskr Laeger, 142(23):1487-90 (1980); Moheb MA, Geissler CA, Lancer K., *Effect of Ephedrine, Caffeine, and Aspirin, in Combinations of Weight Loss in Obese Women*, Int. J. Obes. Relat. Metab. Disord., 22:(Suppl 3):S264 (Abstract) (1998); Pasquali R., Baraldi G., Cesari MP, Melchionda N., Zamboni M., Stefanini C., et al., *A Controlled Trial Using Ephedrine in the Treatment of Obesity*. Int. J. Obes., 9(2):93-8 (1985); Quaade F., Astrup A., Breum L., Toubro S., Hein P., *The Effect of an Ephedrine/Caffeine Combination as a Supplement to a Weight Reducing Diet. A randomized, placebo controlled, double-blind trial*, Ugeskr Laeger, 154 (18):1258-63. 77 (1992).

⁸⁸ Astrup A., Buemann B., Christensen NJ, Toubro S., Thorbek G., Victor OJ, et al., *The Effect of Ephedrine/Caffeine Mixture on Energy Expenditure and Body Composition in Obese Women*, Metabolism, 41(7):686-8 (1992); Buemann B., Marckmann P., Christensen NJ, Astrup A., *The Effect of Ephedrine plus Caffeine on Plasma Lipids and Lipoproteins During a 4.2 MJ/day Diet*, Int. J. Obes. Relat. Metab. Disord., 18(5):329-32. 103 (1994); Daly PA, Krieger DR, Dulloo AG, Young JB, Landsberg L., *Ephedrine, Caffeine and Aspirin: Safety and Efficacy for Treatment of Human Obesity*, Int. J. Obes. Relat. Metab. Disord., 17 (Suppl 1):S73-8 (1993); Jensen, *supra* note 87; Kalman DS, Colker CM, Shi Q, Swain MA. *Effects of a Weight-loss Aid in Healthy Overweight Adults: Double-blind, Placebo Controlled Clinical Trial*, Curr. Therapeut. Res., 61(4):199-205 (2000); Kettle R., Toubro S., Astrup A., *Ephedrine/Caffeine Enhances Abdominal Fat Loss in Females*, Intl. J. Obesity Related Metabolic Disorders, 22 (Suppl 3):S264 (1998); Malchow-Mollo A., Larsen S., Hey H., Stokholm KH, Juhl E. Quaade F., *Ephedrine as an Anorectic: the Story of the 'Elsinore Pill.'* Int. J. Obes., 5(2):183-7 (1981); Moheb, *supra* note 87; Molnar D., Torok K., Erhardt E., Jeges S., *Safety and Efficacy of Treatment with an Ephedrine/Caffeine Mixture. The First Double-blind Placebo-Controlled Pilot Study in Adolescents*, Int. J. Obes. Relat. Metab. Disord., 24(12):1573-8 (2000); Quaade, *supra* note 87; Roed P., Hansen PW, Bidstrup B., Kaern M., Helles A., Petersen KP, *Elsinore Banting Tablets. A Controlled Clinical Trial in General Practice*, Ugeskr Laeger, 142(23):1491-5 (1980); Van Mil E., Molnar D., *Drug Treatment in Obese Adolescents*, Int. J. Obes., 24:(Suppl 1):S184(Abstract) (2000).

⁸⁹ Jensen, *supra* note 87; Moheb, *supra* note 87; Quaade, *supra* note 87.

⁹⁰ Donikyan LA, *A Double Blind Randomized, Placebo-Controlled, Multicenter Clinical Study to Evaluate the Safety and Efficacy of a Natural Herbal Formulation when Taken as Recommended for Weight Control*, Technical Report Version #1, Boca Raton, Fl., Rexall Sundown (2002) (unpublished work).

⁹¹ Boozer CN, Daly PA, Homel P., Solomon JL, Blanchard D., Nasser JA, et al., *Herbal Ephedra/Caffeine for Weight Loss: a 6-Month Randomized Safety and Efficacy Trial*, Int. J. Obes. Relat. Metab. Disord., 26(5):593- 604 (2002); Boozer CN, Nasser JA, Heymsfield SB, Wang V., Chen G, Solomon JL, *An Herbal Supplement Containing Ma Huang-Guarana for Weight Loss: a Randomized, Double-Blind Trial*, Int. J. Obes. Relat. Metab. Disord., 25(3):316-24 (2001); Colker CM, Swain MA, Lynch L., *A Pilot Study Evaluating the Effects of an Ephedrine and Forskolin-based Product on Body Weight and Body Composition in Overweight, Healthy Women*, J. Am. Coll. Nutr., 20(5):a98(Abstract) (2001); Greenway F., deJonge L., Blanchard D., et al., *Evaluation of a Dietary Herbal Supplement Containing Caffeine and Ephedrine on Metabolic Rate, Body Composition, Serum Lipids and Tolerability*, Pennington Center, Louisiana State University (unpublished Work).

(2) Ephedra v. Placebo

RAND identified one clinical trial that assessed the effects of herbal ephedra versus placebo on weight loss.⁹² The results indicated that over a period of three months, those in the ephedra arm lost 1.8 more pounds per month than those in the placebo arm. This result was found to be similar to the effects reported in the studies of ephedra / caffeine combinations.

(3) Ephedra Plus Caffeine v. Placebo

After reviewing four clinical trials assessing the effects of ephedra and herbs containing caffeine, the RAND Report concluded that the combination of ephedra and caffeine is “associated with a statistically significant increase in weight loss per month of 2.1 pounds compared to that of placebo, for up to four months duration.” The Report further stated that there are no significant differences between ephedrine alone, ephedrine plus caffeine, and ephedra plus herbs containing caffeine.

One study examined the long-term safety and efficacy for weight loss of an herbal ephedra and kola nut supplement (90mg ephedrine alkaloids/192mg caffeine/day).⁹³ The study was a six-month randomized, double-blind placebo-controlled trial and involved 167 patients. The study found a significant decrease in body weight, body fat, and LDL-cholesterol. Overall, the average weight loss was -5.3 ± 5.0 kg,⁹⁴ compared to -2.6 ± 3.2 kg⁹⁵ for placebo ($p < 0.001$).

Another study (from the Columbia University College of Physicians and Surgeons) assessed the effects of the herbal supplement Metabolife 356 (72mg ephedrine group alkaloids/day and 240mg caffeine/day).⁹⁶ This was an eight-week randomized, double-blind placebo-controlled study. The study concluded that the product was effective for short-term weight and fat loss in healthy overweight subjects. The treatment group produced significantly

⁹² *Donikyan, supra* note 90.

⁹³ *Boozer and Daly, supra* note 91.

⁹⁴ -11.68 ± 11.02 lbs.

⁹⁵ -5.73 ± 7.06 lbs.

⁹⁶ *Boozer and Nasser, supra* note 91.

($p < 0.005$) greater weight loss (-4.0 ± 3.4 kg)⁹⁷ and fat loss ($-2.1 \pm 3\%$) over the treatment period than did placebo (-0.8 ± 2.4 kg).⁹⁸

b) Safety Findings

(1) Clinical Studies

Significantly, the RAND Report found that no “serious adverse events” were reported in the 52 clinical trials of Ephedra Supplements and ephedrine that were analyzed for safety (the “Trials”).⁹⁹ The Report noted that, in the aggregate, the Trials had significant statistical power only to detect a serious adverse event rate of 1 in a 1000 given the small number of patients studied in the Trials, but that by conventional definition, a [serious] adverse event at that rate would be considered “rare.”¹⁰⁰ Many prescription drugs receive their new drug approvals following trials involving far fewer subjects.

The absence of “serious adverse events” in the Trials is significant because trials are generally conducted in a controlled setting, with much greater certainty that label directions are properly followed and that patients are properly screened prior to the trial and are monitored throughout the trial.¹⁰¹ This data suggests that ephedra is safe when used as directed. It also stresses the importance of ensuring that Ephedra Supplements are properly labeled with warnings and dosage instructions so that consumers are fully informed on the proper usage of the product.

RAND did find sufficient evidence from short-term controlled trials to conclude that the use of ephedrine and/or the use of ephedra or ephedrine plus caffeine is associated with two to three times the risk of nausea, vomiting, and psychiatric symptoms such as anxiety and change in mood, autonomic hyperactivity, and palpitations.¹⁰² RAND notes, however, that it is not

⁹⁷ -8.18 ± 7.49 lbs.

⁹⁸ 1.76 ± 5.29 lbs.

⁹⁹ *The RAND Report*, p. 88.

¹⁰⁰ *Id.*

¹⁰¹ *Id.*

¹⁰² *The RAND Report* p. 202-203; RAND found a statistically significant increase (between 2.15 and 3.64%) in the odds of these side effects, *Id.* p 87.

possible to separate out the contribution of caffeine to these events.¹⁰³ RAND further notes that the increase of reports of hypertension and headaches was not statistically significant.¹⁰⁴ This contradicts the misinformation that has been included in many media stories concerning ephedra.¹⁰⁵ Nevertheless, NVE Pharmaceuticals acknowledges that ephedra is a stimulant that may cause a number of possible side effects and, like any other pharmacologically active substance, can become dangerous if misused. Ephedra Supplements must therefore be used responsibly and as directed. As such, NVE Pharmaceuticals fully supports strong (but not unreasonable) warnings on the product label.

(2) Case Reports

A number of case reports regarding Ephedra Supplements and ephedrine have been filed with FDA. Many of these reports were solicited by FDA. For the most part, RAND found that these reports are insufficiently documented to make an informed judgment about the relationship between the use of Ephedra Supplements or ephedrine and the adverse event in question.¹⁰⁶

After analyzing all of the case reports, including those that were admittedly insufficient, RAND was unable to conclude that there is a cause and effect relationship between Ephedra Supplements or ephedrine and either “adverse events” or “serious adverse events.” It was able to identify, however, two (2) deaths, four (4) myocardial infarctions, nine (9) cerebrovascular accidents, one (1) seizure, and five (5) psychiatric cases as “sentinel events” with prior ephedra consumption; and three (3) deaths, two (2) myocardial infarctions, two (2) cerebrovascular accidents, one (1) seizure, and three (3) psychiatric cases as “sentinel events” with prior ephedrine consumption. Again, it is crucial to note that the classification of a “sentinel event”

¹⁰³ *Id.* p 203.

¹⁰⁴ *The RAND Report* p. 87.

¹⁰⁵ FDA, however, has chosen not to include this information in any of its public statements.

¹⁰⁶ Actually, the majority of the case reports analyzed by RAND were reports made to Metabolife, one of the largest manufacturers of Ephedra Supplements. Similar to FDA’s case reports, RAND concluded that nearly all of Metabolife’s reports were too poorly documented to permit it to make any judgments about the potential relationship between ephedra use and the event reported.

does not imply a proven cause and effect relationship between the ephedra supplement and the adverse event.¹⁰⁷

RAND identified forty-three (43) additional cases as “possible sentinel events” with prior ephedra consumption and eight (8) additional cases as “possible sentinel events” with prior ephedrine consumption. However, as a “possible adverse event,” another condition, by itself, could have caused the event identified.¹⁰⁸

These results provide the background for including strong warnings on the outer packaging of Ephedra Supplements. They do not, however, come close to supporting an outright ban on Ephedra Supplements – especially in light of RAND’s conclusion that Ephedra Supplements are effective in weight management.

(3) FDA Misrepresents Safety Data

Despite these findings, FDA’s press release stated that the RAND Report “adds significantly to the evidence suggesting that ephedra as currently marketed may be associated with unreasonable safety risks.” This gross misrepresentation of the data is disturbing and raises questions as to FDA’s true intent. **How can FDA make this statement when RAND never drew the same conclusions? Why would FDA refuse to acknowledge the RAND Report’s findings, unless the results did not fit the Agency’s predetermined agenda?** While RAND did associate ephedra with certain known side effects, this association does not make the product unreasonably dangerous, especially when the significant public health benefits of the product’s known weight loss effects are taken into full consideration. Furthermore, RAND specifically acknowledged that issues concerning causation between ephedra and adverse events remain unresolved.

¹⁰⁷ *The RAND Report* p. 89.

¹⁰⁸ *Id.*

Moreover, the media and various public figures continue to misrepresent the number and severity of AERs potentially attributable to ephedra. For example, on April 1, 2003, Representative Henry A. Waxman, in his keynote address to the Food and Drug Law Institute (FDLI), stated that FDA is in possession of evidence demonstrating that 100 deaths were “probably caused” by ephedra. Ullman, Shapiro & Ullman, LLP has called on Rep. Waxman to identify the additional 98 cases that were not identified by RAND in its Report, which is purported to be a comprehensive review of the public literature and all evidence in the possession of FDA. A copy of this letter is attached hereto. **NVE Pharmaceuticals calls on FDA to once and for all either repudiate this claim or disclose with precision the adverse events to which Rep. Waxman is referring.**

c) Dosage Findings

In response to specific questions by FDA concerning the relationship between dose and likelihood of adverse events, RAND stated that such an analysis is not justified because 1) **it assumes a cause and effect relationship that has not been proven by conventional standards of medical science**, 2) it would rely on patients’ recall of dose after suffering an adverse event, which increase likelihood of recall bias, and 3) in more than half of the adverse event cases, no dose data was available.¹⁰⁹

4. Issues Relating to RAND Safety Analysis

The RAND Report has a number of limitations, many of which were specifically mentioned in the Report, and potential biases towards finding adverse events. Even so, the weight of the evidence suggests that ephedra is safe when used responsibly.

a) Methods and Safety Conclusions

RAND’s approach admittedly allowed for potential over-counting of patients experiencing adverse events and may have under-counted the number of patients for whom a

¹⁰⁹ *The RAND Report*, p. 32.

particular adverse event was not observed. RAND counted each adverse event as if it represented a unique individual although a single individual might have experienced more than one adverse event. It also did not assume zero adverse events if the trial did not mention a certain type of event or any event at all, but instead excluded these trials from its meta analysis.¹¹⁰

In observing these tendencies (of over and under counting) by the authors, it is interesting to note that, in reviewing the work of others, they noted: Publication bias may occur because of investigators' loss of interest in the study if negative results are found or if results obtained that are contrary to the interest of the sponsor.¹¹¹ In this context, it can be observed that the sponsor of the RAND Report was FDA.

b) Specific Serious Event Reports Cited by RAND

RAND dedicated a portion of its Report to describing specific case reports. These reports were classified by event type, source material, product allegedly taken and by RAND's own self-described categories (i.e. "sentinel," "possible sentinel," etc.). An analysis of several of these events reveals reasonable alternate causes of death and provides strong evidence that the product was not taken as directed on the label.

(1) Case Report #1 (FDA/Ephedrine)¹¹²

This report describes the death of a 33-year-old male taking an OTC ephedrine product, not a dietary supplement. The deceased's blood ephedrine level was listed as "13.4 µg/ml." This amount of ephedrine in the blood clearly indicates an overdose, whether accidental or otherwise. A single oral dose of 24 mg of ephedrine produces an average peak plasma

¹¹⁰ *The RAND Report*, pp. 24-25.

¹¹¹ *The RAND Report*, p. 215.

¹¹² *The RAND Report*, p. 90.

concentration of 0.10 mg/L.¹¹³ The deceased would have needed to ingest a minimum of 3,216 mg (3.216 g) of ephedrine immediately prior to death to achieve that level in his blood. As the maximum level of ephedrine permitted in an OTC tablet is 25 mg, he must have taken at least 128 tablets. This case suggests a clear misuse of an OTC product and should not be considered an event by which to judge the safety of Ephedra Supplements.

(2) Case Report #2 (FDA/Ephedrine)¹¹⁴

This report describes a 30-year-old female who was taking “mini tabs” to loose weight. The amount of ephedrine found in her blood was excessively high at 24 mg/L. Like case report #1 discussed above, this ephedrine level can only be achieved through overdosing.¹¹⁵ This case also suggests the clear misuse of a properly labeled OTC product.

(3) Case Report #3 (FDA/Ephedrine)¹¹⁶

Again, RAND describes the clear misuse of an OTC ephedrine and guaifenesin product as a “sentinel” event. The OTC monograph for ephedrine sets the maximum daily dose at 150 mg. RAND reports that the deceased consumed up to four times this dose (600 mg) on a daily basis. Apparently he only consumed 250 mg on the date of death. Regardless, 250 mg is a clear misuse of the product as labeled and, as such, this event should not be used as a basis to condemn the safety of Ephedra Supplements.

(4) Case Report #4 (FDA/Ephedra)¹¹⁷

This report classified the death of a 15-year-old girl as a “possible sentinel” event even though her autopsy revealed a previously unknown congenital heart defect, Bland-White-Garland Syndrome, which if left untreated, as it was in this case, death is likely in childhood or

¹¹³ Goldfrank LR, Flomenbaum NE, Lewin NA, Weisman RS, Howland MA, *Toxicological Emergencies* 4th ed, 422 (1990).

¹¹⁴ *Id.*

¹¹⁵ Approximately 230 tablets of a 25 mg OTC ephedrine product.

¹¹⁶ *Id.*

¹¹⁷ *The RAND Report*, p. 91.

adolescence.¹¹⁸ How can this event be classified as “possible sentinel” when it seems rather unlikely that there was any other cause of death apart from the heart defect. Furthermore, Ephedra Supplements are not intended to be used by persons under the age of eighteen.

5. No Support that Ephedra is an Unreasonable Risk

The RAND Report is the most recent of a long line of reports written by prominent experts in the scientific community addressing the safety of Ephedra Supplements.¹¹⁹ These reports have generally incorporated data from the scientific literature, case reports and clinical studies in order to perform their analysis and to draw their conclusions. **While the methodologies used in these reports may have differed, the conclusions reached were always similar and are as follows: ephedra and ephedrine group alkaloids do not present a significant or unreasonable risk of illness or injury when used as directed on product labeling bearing responsible warnings and dosage information. Nor does ephedra present an imminent hazard to public health or safety.** Furthermore, the enormous public health benefit (weight loss) served by products containing ephedra and ephedrine alkaloids far outweighs the low incidence of risk, which has been associated with these products.

The generally accepted definition of safety for a drug, which is equally applicable to dietary supplements or to food, is a low incidence of adverse reactions or significant side effects under appropriate conditions of use, and a low potential for harm, which might result from abuse situations.¹²⁰ Furthermore, safety is a relative concept and can only be assessed against the yardstick of normal conditions of use, whether defined (as in label directions) or are implied or traditional. The concept of safety taken out of context thus becomes meaningless.

¹¹⁸ It has been reported that the coroner's office made a statement a week or so after her death that exonerated ephedra, See Natural Nutritional Foods Association (NNFA) Fax update, *Dietary Supplement Not to Blame for Death in Ventura* (June 9, 1998).

¹¹⁹ See V(A)(1) Studies and Expert Reports

¹²⁰ Jones, D., *supra* note 75.

RAND has only found 22¹²¹ “sentinel” events associated with Ephedra Supplements¹²² and at least 3 may have involved serious issues concerning misuse or abuse of the product or usage in contravenes to explicit label warnings. Such a number, when placed in the context of a product consumed in millions of doses, does not indicate that Ephedra Supplements are unreasonably dangerous or pose an imminent hazard to the American people. In addition, RAND adds that further “scientific studies (not additional case reports) are necessary to assess the possible association between consumption of ephedra-containing dietary supplements and these serious adverse events.”¹²³ RAND said it best when it stated “Given the rarity of such [serious adverse] events, a properly designed case control study would be the appropriate next step.”¹²⁴

6. FDA’s Failure to Acknowledge Benefits for Weight Loss and Other Health Benefits.

Despite FDA’s misrepresentations, RAND supports the conclusion that ephedra, when marketed and used responsibly, can provide a significant public health benefit by assisting people in losing statistically significant amounts of weight, even if only for a short-term regimen. The benefit is even greater when you consider the known health risks associated with overweight and obesity as well as the lack of alternative treatments. There are no OTC drugs available for weight loss. Prescription drugs (*e.g.* Sibutramine¹²⁵ and Phentermine¹²⁶) are available, primarily as a treatment for obesity, but are generally more expensive,¹²⁷ more difficult

¹²¹ RAND indicated 21 “sentinel events” associated with prior ephedra consumption.

¹²² RAND found 9 (not 11 as indicated) “sentinel events” associated with prior ephedrine consumption and at least 5 of those also involved serious issues concerning misuse or abuse of the product or usage in contravenes to explicit label warnings.

¹²³ *The RAND Report*, p. 203.

¹²⁴ *Id.*

¹²⁵ Meridia manufactured by Abbott Labs.

¹²⁶ Adipex manufactured by Gate Pharmaceuticals.

¹²⁷ Sibutramine (Meridia[®]) can cost as much as \$4.00 per capsule (15mg); Phentermine (Adipex[®]) can cost as much as \$2.00 per capsule (37.5mg) and Orlistat (Xenical[®]) can cost over \$1.00 per capsule (120mg).

to obtain and are often associated with greater health risks.¹²⁸ Although surgery is an option for seriously obese individuals, it is associated with much greater health risks as well as significant costs.

a) Significant Public Health Benefit

RAND reports that in 2000, the majority (56%) of Americans were overweight¹²⁹ and in 2002, 19.8% of Americans were obese.¹³⁰ And these numbers are increasing. Obesity among adults has doubled since 1980, and the number of overweight adolescents has tripled.¹³¹ From 1999 to 2002, the prevalence of obesity in the U.S. has risen 1% each year.¹³² As HHS Secretary, Tommy G. Thompson, has stated, “overweight and obesity are among the most pressing new health challenges we face today ... Our modern environment has allowed these conditions to increase at alarming rates and become a growing health problem for our nation. By confronting these conditions, we have tremendous opportunities to prevent the unnecessary disease and disability they portend for our future.”¹³³

Overweight and obesity refer to increased amounts of body fat, commonly assessed by the body-mass index (“BMI,” calculated as weight in kilograms divided by height in meters squared). A BMI score of 18.5 – 24.9 is considered normal, 25 – 29.9 is considered overweight, and over 30 is considered obese. A higher BMI, beginning in the upper range of the normal

¹²⁸ Phentermine - There have been rare cases of Primary Pulmonary Hypertension (PPH) (a rare, frequently fatal disease of the lungs) in patients taking Phentermine alone; the possibility of association cannot be ruled out. Serious regurgitant cardiac valvular disease, primarily affecting the mitral, aortic and/or tricuspid valves, has been reported in otherwise healthy persons in patients taking Phentermine alone; the possibility of association cannot be ruled out. Physicians Desk Reference, p. 1407 (2002) (“PDR”); Sibutramine – This drug substantially increases blood pressure in some patients. Accordingly, regular monitoring of blood pressure is required when prescribed Sibutramine. No cases of PPH were reported in trials, but it is not known whether or not Sibutramine may cause the disease. *Id.* at 481.

¹²⁹ *The RAND Report*, p. 5, citing Mokdad AH, Bowman BA, Ford ES, Vinicor F., Marks JS, Koplan JP, *The continuing epidemics of obesity and diabetes in the United States*, JAMA, 284(13):1650-1 (2000).

¹³⁰ A recent assessment by the London-based International Obesity Task Force indicated that up to 1.7 billion persons worldwide could be overweight or obese. Post-Gazette National Bureau (March 17, 2003).

¹³¹ U.S. Department of Health and Human Services. *The Surgeon General's call to action to prevent and decrease overweight and obesity*. [Rockville, MD]: U.S. Department of Health and Human Services, Public Health Service, Office of the Surgeon General; (2001). (“The Surgeon General Report”).

¹³² *The RAND Report*, p. 5.

¹³³ U.S. Food and Drug Administration, FDA Consumer magazine (March-April 2002).

weight category, is associated with increased mortality and increased risk for coronary heart disease, osteoarthritis, diabetes mellitus, hypertension, and certain types of cancer.¹³⁴ A recent paper by Roland Sturm, a senior economist at RAND, concluded that the effects of obesity on the number of chronic conditions are significantly larger than the effects of current or past smoking or problem drinking.¹³⁵ The paper further stated that the effects of smoking or problem drinking are similar to those of being overweight.¹³⁶

There are a myriad of public health benefits associated with the loss of 5 to 11% of a person's total body weight, which was found to be associated with the use of ephedra. Studies have shown that even modest weight reduction can have substantial lifetime health benefits.¹³⁷ The U.S. National Institute of Diabetes & Digestive and Kidney Diseases of the National Institute of Health states on its public Internet website that "losing as little as 5 to 10% of your body weight may improve many of the problems linked to being overweight, such as high blood pressure and diabetes."¹³⁸ Moreover, RAND indicated in its Report that "intentional weight loss by obese persons leads to reductions in risk factors for disease" and that "a minimum loss of 5 to 10 percent of body weight followed by long term weight maintenance can improve health outcomes."¹³⁹ Why wouldn't FDA want to reduce the approximately 300,000 U.S. deaths each year that are associated with being overweight (compared to more than 400,000 deaths per year associated with cigarette smoking), or reduce the total direct and indirect costs attributed to persons being overweight, which amounted to \$117 billion in the year 2000 alone?¹⁴⁰

¹³⁴ Sturm, R., p. 246. *supra* note 5 .

¹³⁵ $p < .001$. *Id.*

¹³⁶ Not statistically different from each other, although significantly different from 0 at $p < .05$, except past smoking, $p = .1$. *Id.* at 248.

¹³⁷ *Id.* at 248; See also *The RAND Report*, p. 6.

¹³⁸ United States National Institute of Diabetes & Digestive and Kidney Diseases of the National Institute of Health. See <http://www.niddk.nih.gov/health/nutrit/pubs/health.htm#how>.

¹³⁹ *The RAND Report*, p. 6, citing *NIH Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults*. The Evidence Report. *Obes Res.* 6(Suppl 2):51S-209S (1998).

¹⁴⁰ *The Surgeon General Report*, *supra* note 131.

b) More Effective than Some Prescription Drugs

The proven effects of Ephedra Supplements on weight loss are even greater than certain prescription weight loss products on the U.S. market today. Placebo controlled trials of the FDA – approved weight loss pharmacotherapies, Sibutramine or Orlistat¹⁴¹ have shown losses of 6-10 pounds more than placebo, over 6-12 months. Another approved drug, Phentermine, has shown losses of 16 pounds more than more than placebo at 9 months. A simple data comparison shows that the proven benefits of Ephedra Supplements are comparable to all three prescription drugs mentioned herein. FDA’s refusal to acknowledge the potential significance of this data is inexplicable.

c) No OTC Alternative

Adding further significance to the need for Ephedra Supplements is the fact that there is no approved OTC remedy on the market for weight loss.

d) FDA Misrepresents Efficacy Data

Despite RAND’s identification of a significant potential public health benefit associated with Ephedra Supplements, FDA has continued to denigrate this herb and the products that contain it, in an obvious effort to undermine DSHEA. FDA’s press release, HHS Acts to Reduce Safety Concerns Associated with Dietary Supplements Containing Ephedra Fact Sheet,¹⁴² which was circulated the same day as the RAND Report and the Agency’s proposed regulations for ephedra, states that the RAND Report found “limited evidence of an effect of ephedra on short-term weight-loss.” However, the Report expressly states that:

“the evidence we [RAND] identified and assessed supports the following conclusions: The short-term use of ephedrine, ephedrine plus caffeine, or the assessed dietary supplements containing ephedra and herbs with caffeine is associated with a statistically significant increase in short-term weight loss (compared to placebo).”¹⁴³

¹⁴¹ Xenical manufactured by Hoffmann-La Roche, Inc.

¹⁴² February 28, 2003.

¹⁴³ *The RAND Report*, p. 201.

As noted earlier, the studies examined by RAND actually indicate a weight loss of approximately two pounds per month greater than that of placebo or a range of 5 to 11 percent reduction in pretreatment weight. These numbers, which equate to more than 12 pounds over a six-month period should be celebrated by our public health agencies, not misrepresented and suppressed.

FDA's failure to acknowledge the efficacy data, as well as the safety data, suggests that FDA has a specific agenda. Why else would the FDA misstate the conclusions with regard to efficacy (and safety), if not to build political support for an outright ban, to generate negative media coverage on ephedra in general, as well as to build a case in support of the Agency's efforts to amend or revoke DSHEA? FDA's actions are even more disturbing in light of RAND's suggestion that ephedra is at least as effective as Sibutramine or Orlistat, two FDA-approved prescription drugs for weight loss.

E. Other Efficacy Studies of Commercial Products

Some clinical trials have used commercial products to determine the efficacy of the combination of ephedra and caffeine. One study using the product Xenadrine (40mg/day ephedrine; 400mg caffeine), which examined changes in body mass, % fat, fat mass, and fat-free mass, also indicated a positive effect on body weight.¹⁴⁴ The study involved 14 subjects over a period of six weeks and found that ephedrine/caffeine supplementation resulted in a statistically significant change in fat mass ($p < 0.033$). This study was not included in RAND's efficacy analysis (RAND did not include any studies where the duration of treatment was less than eight weeks).

Another study, presented at the Second Annual Meeting of Exercise Physiologists in 1999, concluded that the product Hydroxycut (29 mg ephedra; caffeine 200; salicin 15mg) was

¹⁴⁴ Armstrong P., Johnson S., Duhme, *The Effect of Commercial Thermogenic Weight Loss Supplements on Body Composition and Energy Expenditure in Obese Adults*, J. of Exercise Physiology Online, Vol. 4, No. 2 (2001).

safe and effective for weight loss.¹⁴⁵ This study was a randomized double-blind, placebo controlled eight week study that examined twenty-four overweight healthy adults. It was shown that treatment plus moderate exercise resulted in a significant reduction in body weight (-3.8 kg¹⁴⁶; p<0.01). Although the study was eight weeks long, RAND did not include this trial in its Report.

V. EPHEDRA IS SAFE WHEN USED AS DIRECTED – ADDITIONAL DATA

Experts who have reviewed all of the available historical and clinical data agree: you can take Ephedra Supplements safely if you adhere to the indicated serving limitations and follow warnings and precautions similar to those adopted by AHPA and industry.¹⁴⁷

A. *Studies and Expert Reports*

1. Ephedra Education Council (EEC) Expert Panel Report¹⁴⁸

The Ephedra Education Council (EEC) is an industry organization that provides science-based information about the safety and effectiveness of dietary supplements containing ephedra. The EEC primarily consists of members of the AHPA Ephedra Committee and seeks to promote safe and responsible marketing of dietary supplements.

In August 2000, a seven-member panel from the EEC presented a consensus report at a hearing held by HHS's Office of Women's Health.¹⁴⁹ The panel consisted of experts from various medical and scientific disciplines.¹⁵⁰ Together, they reviewed the entire public record of more than 1,000 AERs submitted to FDA as well as published scientific literature on the safety

¹⁴⁵ Colker C.M., Torina G.C., Swain M.A., Kalman D.S., *Double-blind placebo controlled evaluation of the safety and efficacy of ephedra, caffeine, and salicin for short-term weight reduction in overweight subjects*, Department of Medicine, Greenwich Hospital, American Society of Exercise Physiologists, 2nd Annual Meeting (1999).

¹⁴⁶ 8.38 lbs.

¹⁴⁷ See AHPA's Role.

¹⁴⁸ Ephedra Education Council, *Comments of the Expert Panel of the Ephedra Education Council on the Safety of Dietary Supplements Containing Ephedrine Alkaloids and on the AERs and the Health Assessments Released by the FDA on April 3, 2000* (Sept. 29, 2000).

¹⁴⁹ *Ephedra Hearing*, *supra* note 46.

¹⁵⁰ Stephen E. Kimmel, M.D.; Steven B. Karch, M.D.; Norbert P. Page, M.S., D.V.M.; Theodore Farber, Ph.D., DABT; John W. Olney, M.D.; Edgar H. Adams, M.S., Sc.D.

of ephedra. The EEC expert panel consensus report represented a comprehensive review of ephedra safety issues.

The EEC panel reached several important conclusions:

- Dietary supplements containing ephedra should contain appropriate directions and warnings.
- Ephedra dietary supplements are not associated with any serious adverse events when used according to industry recommendations (*i.e.* serving limits of 25 mg per serving and 100 mg per day and appropriate warnings).
- Dietary supplements containing ephedra and caffeine may be useful in weight management.
- Severe overdosing can lead to serious adverse reports.
- Ephedra supplements do not appear to be the cause of the death in the AERs reported to FDA.
- Additional studies are needed in order to address any unresolved issues.
- Products marketed as “street drug alternatives” should be prohibited because they promote excessive use and abuse.

In addition to the consensus report, individual members also issued individual statements to FDA regarding the safety of ephedra.

2. The Cantox Report: Safety Assessment and Determination of a Tolerable Upper Limit for Ephedra¹⁵¹

Cantox Health Science International, an internationally recognized scientific research organization, prepared a report in December 2000 for the Council for Responsible Nutrition. The "Cantox Report" reviewed the available information related to the safety of ephedra/ephedrine alkaloids and established a safe upper intake limit (UL) based on the National Academy of Sciences upper intake limit model for nutrients. At the time, this report was the only formal risk assessment that had been done for dietary supplements containing Ephedra. Cantox established an upper intake limit of 90mg of ephedrine alkaloids per day for a generally healthy population (“This daily level of intake is unlikely to pose a risk of adverse health effects”). The report further concluded that the upper intake limit does not apply to specific

¹⁵¹ Cantox Health Sciences International Report, *Safety Assessment and Determination of Tolerable Upper Limit for Ephedra*, Council for Responsible Nutrition (Dec. 19, 2000). [hereinafter *The Cantox Report*].

groups of persons and that no single dose should exceed 30mg. The Cantox Report confirms that the industry standards established by AHPA (100mg/day; 25mg/dose) are reasonable and substantiated by scientific literature.

3. The Harvard/Columbia Study: Herbal Ephedra/Caffeine for Weight Loss: A 6-Month Safety and Efficacy Trial¹⁵²

This study examined the long-term safety and efficacy for weight loss of an herbal supplement containing *ma huang* and kola nut (30mg ephedrine alkaloids, three times per day).¹⁵³ It was a six-month randomized, double-blind placebo controlled trial, the results of which were published in the May 2002 issue of the International Journal of Obesity (IJO). After six months, “the tested product produced *no adverse events* and *minimal side effects* that are consistent with the known mechanisms of action of ephedrine and caffeine.” [emphasis added]

4. The Greenway Article: The Safety and Efficacy of Pharmaceutical and Herbal Caffeine and Ephedrine Use as a Weight Loss Agent¹⁵⁴

This article by Dr. Frank Greenway, an internationally recognized expert and researcher in bariatric medicine¹⁵⁵ from the Pennington Biomedical Research Center, reviewed more than 100 articles in the Medline database published from 1966 through 2000 on the effects of ephedrine and caffeine on weight loss. Dr. Greenway concluded that “there have been a relatively small number of serious adverse events reported to a surveillance system in response to government requests to do so, compared with the widespread use of herbal products containing caffeine and ephedra.” Dr. Greenway also noted that voluntary case reports, having no denominator with which to calculate incidence and no control group with which to compare, are not an objective method upon which to restrict the use of herbal products containing caffeine and

¹⁵² *Boozer and Daly, supra* note 91.

¹⁵³ The favorable results of this trial were included in *The RAND Report* and are discussed therein.

¹⁵⁴ Greenway F., *Safety and Efficacy of Pharmaceutical and Herbal Caffeine and Ephedrine use as a Weight Loss Agent*, *Obesity Reviews*, 2:199-211 (2001).

¹⁵⁵ A bariatric doctor is a doctor who specializes in treating overweight and obesity and its associated conditions.

ephedrine.” Overall, he found that “the benefits of ephedrine and caffeine in treating obesity appear to *outweigh the small associated risks.*” [emphasis added]

5. Summary of Incidence of Seizures, Strokes, and Myocardial Infarctions in the Population and Estimations of Risk in the Population from Ephedra Products (Stephen E. Kimmel, M.D)¹⁵⁶

Dr. Stephen Kimmel, chair of the EEC Expert Panel, compared the incidence of seizures, strokes, and heart attacks in users of dietary supplements containing ephedrine alkaloids to the incidence of those events in the general population. Dr. Kimmel estimated the number of events among ephedra users by using the number of events reported to FDA, even including those reports that FDA conceded had insufficient data from which to analyze the event or in which the user had abused the product. To account for any possibility of underreporting, Dr. Kimmel used a range of 1% to 20% of reported events, and a conservative estimate of approximately 2.8 to 11 million consumers of ephedra products. Dr. Kimmel found that the risk of seizure, stroke or heart attack was not greater in ephedra users than in the general population. Dr. Kimmel further noted that FDA had failed to include any assessment of background risk in its evaluation of ephedra safety.

6. Ad Hoc Committee on Safety of *Ma Huang* (Dr. Dennis Jones; Herb Research Foundation)¹⁵⁷

In response to the Texas Department of Health’s proposed regulation of ephedra products, the Committee presented two comprehensive safety studies of *ma huang* and ephedrine to prove that the Texas proposals lacked any scientific basis. After reviewing 150 articles from over 20 scientific journals, Dr. Jones concluded that ephedra dietary supplements are safe when used in accordance with appropriate directions.

¹⁵⁶ Stephen Kimmel, *Summary of Incidence of Seizures, Strokes, and Myocardial Infarctions in the Population and Estimations of Risk in the Population from Ephedra Products*, presented at the *Ephedra Hearing* on Aug. 8 & 9, 2000.

¹⁵⁷ Jones, *supra*, note 75.

B. Reference Texts.

As noted earlier, ephedra has been used in traditional medicine for over 5,000 years and is currently listed in the official Pharmacopoeias of Germany, Japan, and China. Recommended doses (as well as daily limits) have been established by The British Herbal Pharmacopoeia,¹⁵⁸ the AHPA Botanical Safety Handbook,¹⁵⁹ and the German Commission E Monographs.¹⁶⁰ The recommended dose generally falls between 15-30mg total ephedrine alkaloids, with a daily limit of approximately 300mg.

VI. AHPA's Role

A. Introduction

The American Herbal Products Association, a national trade organization founded in 1983, is a recognized leader in representing the responsible center of the botanical trade and its members include the finest growers, processors, manufacturers and marketers of herbal products. AHPA's number one mission has always been to promote responsible commerce of herbal products through self-regulation. The organization has also taken an active role in the marketing of ephedra.

AHPA adopted standards many years ago as a recommendation to distributors, marketers, and consumers of dietary supplement products containing ephedrine alkaloids (the "Standards"). A panel of experts from a variety of scientific and medical backgrounds endorsed the Standards that AHPA established. In addition, several states, including Ohio, Michigan, Nebraska, Texas, Oklahoma, Hawaii, Washington and California, have adopted portions of these Standards as state law.

¹⁵⁸ *British Herbal Pharmacopoeia*, British Herbal Medicine Association, 82-83 (1983).

¹⁵⁹ McGuffin, M., C. Hobbs, R. Upton, A. Goldberg, American Herbal Product Association's *Botanical Safety Handbook*, Boca Raton, CRC Press (1997).

¹⁶⁰ Blumenthal M., Busse WR, Goldberg A., Gruenwald J., Hal T., Riggins CW, Rister RS (Eds.), Kelin S., Rister RS (trans.), *The Complete German Commission E Monographs – Therapeutic Guide to Herbal Medicines*, Austin, TX, American Botanical Council; Boston, Integrative Medicine Communications (1998).

B. History of AHPA re: Ephedra

1. March 1994

In March 1994, the AHPA Board of Trustees recommended the following cautionary statement and a prohibition against the use of Ephedra Supplements by children less than 13 years of age.

Seek advise from a health care practitioner prior to use if you are pregnant or nursing, or if you have high blood pressure, heart or thyroid disease, diabetes, difficulty in urination due to prostate enlargement, or if taking an MAO inhibitor or any other prescription drug. Reduce or discontinue use if nervousness, tremor, sleeplessness, loss of appetite or nausea occur. Not for children under 13. Keep out of the reach of children.

2. January 1995

In January 1995, the Board revised the cautionary statement to raise the prohibition age to 18. The Board also added a prohibition against synthetically derived ephedrine alkaloids.

3. September 1995

The Board approved three modifications as follows: (1) the addition of the phrase “*Do not exceed recommended dose*” to the cautionary label statement; (2) the establishment of a requirement that all ingredients containing ephedrine alkaloids (*e.g. ma huang, ephedra and Sida cordifolia*) be labeled by their common name “Ephedra,” with a clarification that *ma huang* may be acceptable parenthetically. This requirement, with the exception of the parenthetical, conforms to current FDA labeling regulations, which require that all dietary ingredients be listed by their standard and common name as listed in *Herbs of Commerce*; and (3) the addition of dosage limits for total ephedrine alkaloids (established at 30 mg per dose and 120mg per day) to the product label.

4. January 1996

The Board revised dosage limits for total ephedrine alkaloids to 20-25mg per dose and 100mg per day.

5. January 2000

The Board approved a number of changes to the cautionary statement and required that the product label list the amount of ephedrine alkaloids per serving. The Board also approved a prohibition against claims that a product may be useful to achieve an altered state of consciousness, euphoria, or can be used as a “legal” alternative to an illicit drug.

6. September 2000

The final changes to AHPA’s cautionary statement were made in September 2000, when AHPA’s Executive Committee approved the addition of the words “Warning” to the beginning of the statement, “glaucoma” to the list of conditions that require prior consultation with a health care provider and the replacement of the term “psychiatric condition” with the “depression or other psychiatric condition.” Furthermore, the Committee added a requirement that the label state the amount of caffeine, if any, in the product.

C. AHPA’s 2000 Petition to FDA

In October 2000, AHPA, along with The Consumer Healthcare Products Association (“CHPA”), The National Nutritional Foods Association (“NNFA”) and The Utah Natural Products Alliance (all together as "trade associations"), submitted a citizen’s petition to request that the Commissioner of FDA withdraw the remaining portions of the 1997 Proposed Rule and adopt and implement in its place the Standards that had been voluntarily and uniformly adopted by the trade associations (the “Citizen Petition”). These trade associations represent the vast majority of the manufacturers and distributors of ephedra products. The Standards proposed were as follows:

Labeling

1. The label of the goods should bear an adequate cautionary statement, which shall at a minimum include the following language, or comparable language:

WARNING: Not intended for use by anyone under the age of 18. Do not use this product if you are pregnant or nursing. Consult a health care professional before using this product if you have heart disease, thyroid disease, diabetes, high blood pressure,

depression or other psychiatric condition, glaucoma, difficulty in urinating, prostate enlargement, or seizure disorder, if you are using a monoamine oxidase inhibitor (MAOI) or any other prescription drug, or you are using an over-the-counter drug containing ephedrine, pseudoephedrine or phenylpropanolamine (ingredients found in certain allergy, asthma, cough/cold and weight control products).

Exceeding recommended serving will not improve results and may cause serious adverse health effects.

Discontinue use and call a health care professional immediately if you experience rapid heartbeat, dizziness, severe headache, shortness of breath, or other similar symptoms.

2. The product label shall list the amount of ephedrine alkaloids and caffeine alkaloids, if present, per serving.

Serving Limits

Products are not to contain in excess of 25mg of total ephedrine alkaloids per serving; usage instructions should limit daily consumption to 100mg of total ephedrine alkaloids.

Herbs of Commerce Conformity

Label identification must be in conformity with the standard common name listed in Herbs of Commerce.

Synthetic Ingredients

Neither finished consumer goods nor raw materials used in their manufacture are to contain any synthetically derived ephedrine alkaloids or their salts (e.g., ephedrine sulfate; pseudoephedrine hydrochloride; phenylpropanolamine hydrochloride).

Marketing

No claims shall be made that the product may be useful to achieve an altered state of consciousness, euphoria, or as a "legal" alternative for an illicit drug.

AHPA further indicated in its Citizen Petition that recent analyses of the safety of ephedra presented at the Ephedra Hearing and submitted to FDA as comments confirm that ephedra products are safe when marketed and consumed according to the Standards. Further, new data presented at the Ephedra Hearing confirmed that Ephedra Supplements provide significant public health benefits in the area of weight loss. The consensus of the Ephedra Hearing, as stated in the HHS's Office on Women's Health Report, was that the industry and the government should work together to educate consumers about ephedra products and to conduct further research into the safety and benefits of these products; AHPA and NVE Pharmaceuticals fully support this position.

AHPA still supports the recommendations in the Citizen Petition. Implementation of such Standards with the additional prohibition of sales or marketing to minors would make it possible for adult consumers to have continued access to these efficacious products while additional research may be pursued to further optimize our understanding of ephedra's safety and benefits.

VII. POSITION WE SUPPORT

A. We Would Not Oppose the Adoption of Strict Warnings as long as They Are Based in True Science and Not Politics

1. FDA's Proposed "Back Panel" Warning

For many years, the natural products industry has supported strong, uniform, science-based, warning language on Ephedra Supplements. As such, NVE Pharmaceuticals fully supports much of what FDA has proposed in its recent proposed "back panel" warning. NVE Pharmaceuticals proposes, however, that certain portions of this warning statement be made stronger, other portions be relaxed and that a number of other provisions be better explained.

a) Proposed Modifications

(1) Medical Conditions

NVE Pharmaceuticals proposes the addition of the following language to the "back panel" warning section listing medical conditions: "You may not know if you have one of these conditions. If you are concerned you should consult your health care provider."

(2) Usage

NVE Pharmaceuticals proposes the addition of the following language or words to similar effect to the end of the "back panel" warning: "Do not abuse this product. Exceeding recommended dose will not improve results." This modification is intended to address the common misconception that if you increase the dose (whether a dietary supplement or a drug) the results will increase proportionately.

(3) Health Care Provider

NVE Pharmaceuticals proposes that the word “doctor” be used throughout the proposed warning be changed to “health care provider.” This modification reflects that there is a growing segment of the population that consults with persons other than doctors (*e.g.* nurse practitioners) for their health care advice.

b) Creative Labeling

Because the “back panel” warning is lengthy and the labels and packaging of Ephedra Supplements are relatively small (even in large bottles such as 100 count), NVE Pharmaceuticals proposes that FDA specifically permit creative labeling solutions, such as peel away labels (both two panel and booklet types) and product inserts to bear all required “back panel” warnings.

2. FDA Proposed Black Box Warning – Front

a) Not Justified

The use of a “black box” warning is normally reserved for adverse reactions associated with use of prescription drug products that may result in death or serious injury.¹⁶¹ It is FDA's most serious warning for a prescription drug. FDA has never mandated use of this type of warning on any OTC product, no matter how serious its potential side effects (*e.g.* Aspirin). Currently, there is no evidence of a cause and effect relationship between ephedra (not a drug) and such adverse events. Therefore, FDA’s proposal for a “black box” warning on the PDP is unreasonable.

Even if a “black box” warning were utilized on Ephedra Supplements, its sole purpose would be to convey a clear message to the prospective user that there have been adverse events reported with the use of the product. Such a message can easily be conveyed in 25 words or less, thus making the warning proposed by FDA further unreasonable and burdensome in that it conveys its message in over 75 words.

¹⁶¹ See 21 C.F.R. 201.57(e).

(1) Examples of Products with Black Boxes

(a) Nolvadex

In 2002, FDA added a black box warning to Nolvadex (tamoxifen),¹⁶² a medication used to reduce the risk of developing breast cancer. FDA determined that a strengthened warning was necessary after new information reported an association between the drug and serious, life-threatening, or fatal events such as uterine malignancies, stroke and pulmonary embolism.

(b) Hormone Replacement Therapy Drugs

FDA has announced that hormone replacement therapy (HRT)¹⁶³ packaging will be required to bear an updated "black-box" warning highlighting recent findings about serious adverse events. The announcement comes in the wake of a recent study, finding that women taking combined HRT (Prempro) had an increased risk of heart disease, breast cancer, stroke, and thrombosis compared with women taking placebo.¹⁶⁴

b) Modified PDP Statement

Nevertheless, NVE Pharmaceuticals is willing to adopt front panel labeling that will alert consumers to adverse events that have been reported, even though such reports have not been conclusively linked to ephedra. NVE Pharmaceuticals' recommended front panel warning is as follows:

WARNING: Contains ephedrine alkaloids. Heart attack, stroke, seizure, and death have been reported after consumption of ephedrine alkaloids. Not for persons under 18. See more information on back panel.

3. Call for National Uniformity

FDA warning should preempt state warnings, many of which require specific language not included in FDA's proposal. Adoption of a strong, science-based warning by FDA will serve

¹⁶² AstraZeneca.

¹⁶³ Prempro, Premarin, and Premphase.

¹⁶⁴ *FDA Approves New Labels for Estrogen and Estrogen with Progestin Therapies for Postmenopausal Women Following Review of Women's Health Initiative Data* (January 8, 2003).

the public health. A statement from the Agency supporting national uniformity will benefit both consumers (by avoiding confusion) and the industry (by providing for reasonable packaging). AHPA has long supported the implementation of a national standard to ensure the safe use of Ephedra Supplements. NVE Pharmaceuticals has effectively implemented this standard in its voluntary program.

4. Call for Responsible Marketing and Education

NVE Pharmaceuticals strongly supports responsible marketing of Ephedra Supplements and is also committed to participating in a public education campaign to alert parents against the use of Ephedra Supplements by children under eighteen and to encourage the safe and responsible use of Ephedra Supplements by adults.

NVE Pharmaceuticals opposes any marketing of Ephedra Supplements as a "legal" alternative for an illicit drug or any marketing indicating the product may be useful to achieve an altered state of consciousness, euphoria, or a "high." Furthermore, NVE Pharmaceuticals opposes the marketing of Ephedra Supplements bearing street drug names.

5. Strict Enforcement using DSHEA

a) Ephedra Is Regulated

The FDA has the specific authority to remove an Ephedra Supplement off the market if it is "adulterated," "misbranded," or if it poses an imminent hazard. Under the FDCA as amended by DSHEA, a dietary supplement that is "adulterated" or "misbranded" or that bears an unauthorized drug claim is subject to seizure, condemnation or destruction.

A product is considered "adulterated" if it bears or contains any poisonous or deleterious substance, which may render it injurious to health.¹⁶⁵ A product is considered "misbranded" if, among other things, it's labeling is false or misleading.¹⁶⁶

¹⁶⁵ See 21 U.S.C. § 342(a)(1).

¹⁶⁶ See 21 U.S.C. §343.

In 1994, the United States Congress passed DSHEA, which amended the Act. DSHEA gave the FDA substantial new policing power to stop the distribution of unsafe dietary supplements. DSHEA expanded the definition of “adulterated” and provides that a dietary supplement or dietary ingredient is adulterated if it 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 or recommended in the labeling, under ordinary conditions of use).¹⁶⁷

A dietary supplement that contains a new dietary ingredient (*i.e.* an ingredient not available in the American food supply prior to October 15, 1994) is adulterated when there is inadequate information to provide reasonable assurance that the ingredient will not present a significant or unreasonable risk of illness or injury.¹⁶⁸ Under the Act, the Secretary of HHS may also declare that a dietary supplement or dietary ingredient poses an imminent hazard to public health or safety, thereby making such dietary supplement or dietary ingredient adulterated.¹⁶⁹ A dietary supplement may also be considered adulterated if it bears or contains any poisonous or deleterious substance, which may render it injurious to health under recommended or suggested conditions of use.

As such, like any other food, it is a manufacturer's responsibility to ensure that its products are safe and properly labeled prior to marketing. Additionally, if a supplement makes drug claims¹⁷⁰ or lacks truthful and informative labeling,¹⁷¹ FDA can remove it from the market.

b) Regulatory Status Distorted by Media

The idea that ephedra, along with all other dietary supplements such as Ginseng and Saw Palmetto, is unregulated by the government is a falsity that has been almost exclusively

¹⁶⁷ See 21 U.S.C. § 342 (f)(1).

¹⁶⁸ See 21 U.S.C. § 342 (f)(1)(B).

¹⁶⁹ See 21 U.S.C. § 342 (f)(1)(C).

¹⁷⁰ See 21 U.S.C. §§ 321(g)(1)(B), 343(r)(6)(C) (FDCA §§ 201(g)(1)(B), 403(r)(6)(C)); 21 C.F.R. § 101.93(f) and (g).

¹⁷¹ See 21 C.F.R. §§ 101.3, 101.4, 101.5, 101.36, 101.105.25.

perpetuated by the media. Even The New York Times and The Washington Post have referred to ephedra as being “largely unregulated” when, in fact, FDA has been regulating dietary supplements for close to one hundred years, as it does foods, drugs, medical devices and cosmetics. The media has consistently interpreted DSHEA to imply that dietary supplements are unregulated simply because these products do not require pre-approval by FDA. However, the fact that the FDA does not pre-approve dietary supplements is of no special significance since FDA does not pre-approve most of the items it regulates, including foods, OTC drugs, and some medical devices. The media also fails to acknowledge that these products are subject to strict labeling requirements and can be taken off the market by FDA if proven not to be safe and effective.

c) DSHEA Is Not the Issue – No Need to Change Law

DSHEA is good law. FDA needs to begin utilizing the broad authority it is provided under the FDCA as amended by DSHEA. When a company attempts to sell an adulterated product, FDA is responsible for taking the appropriate regulatory action against that company and its product. If a company sells a product that causes side effects or adverse events, FDA must investigate. However, it should be noted that the existence of side effects or adverse events does not necessarily make a product unsafe or an imminent danger. Food, for instance, can be dangerous.

(1) Safety of Food – “Food Can Be Dangerous”

(a) Peanuts – “Snickers”

According to researchers, more than 4 million Americans suffer from food allergies and an estimated 150-200 Americans die each year from severe allergic reactions to foods.¹⁷² Some 30,000 emergency room visits per year are also due to food allergies. Interestingly, studies

¹⁷² FDA Consumer Magazine, (July-August 2001).

indicate that the number of people with food allergies is skyrocketing in developed and developing countries but not in underdeveloped countries.

The most common food allergies in adults are shrimp, lobster, crab and other shellfish; peanuts, walnuts and other tree nuts; fish; and eggs. In children, eggs, milk, peanuts, soy and wheat are the most common. While children can outgrow food allergies, adults generally do not. Typical symptoms of allergic reactions include difficulty breathing, hives, vomiting, abdominal cramps, diarrhea, drop in blood pressure, loss of consciousness, and even death. Does the reporting of serious adverse events for these foods such as peanuts mean that the FDA should declare peanuts an imminent hazard and immediately ban the sale of all products that contain peanuts because peanuts can be deadly? Should the FDA propose front panel “black box” labeling on all jars of peanut butter or Snickers’ bars saying “consumption of this product has been reported to cause death?” Of course not. People are expected to read the product labels and to act responsibly. If someone has a peanut allergy, they must not eat that Snickers bar. An ephedra user also must read the product label and understand the expected effects, the side effects and the possible adverse events of the particular product. If the user is concerned or unsure if they have a family history of any of the conditions listed on the label, it is their responsibility to speak with their doctor or licensed health care professional prior to using the ephedra product. Also, if the recommended dose is 2 pills per day, it would be wholly irresponsible and reckless of that person to exceed that dose. In fact, many of the commodities that are a normal part of our daily life, including foods, drugs and dietary supplements, are unsafe and can even become lethal when used in a way that was not intended by the manufacturer or by the regulatory authority that permits them to be a part of our environment. This is why products have labels and warnings. Adults, even professional athletes, are also expected to be responsible in their intake of supplements.

With regard to allergens, legislation has been introduced to make food labeling easier to understand and to help consumers reduce the risks of allergic reactions. Many food manufacturers and trade organizations are currently working with FDA to develop adequate labeling guidelines. The National Food Processors Association developed a voluntary allergen labeling program and a “code of practice.” This type of industry self-regulation in cooperation with the regulatory agencies is key in preserving public safety while allowing foods to remain on the market. Similarly, self-regulation by the dietary supplement industry is key to preserving public safety and educating the public.

DSHEA already regulates the content of supplement product labels and errors or omissions in product labels would make a product “misbranded,” giving FDA the power to take immediate action.

NVE Pharmaceuticals and AHPA support a front panel warning for Ephedra Supplements. Specifically, NVE Pharmaceuticals and AHPA encourage a clear and concise warning statement based on scientific certainties that is designed to allow the public to reap the health benefits of ephedra products with full knowledge of the side effects and possible adverse effects if the product is abused. Even DSHEA anticipated the possible need for warning statements on dietary supplements, as it specifically states that the appearance of a warning statement on a supplement may be appropriate and does not in and of itself indicate that such product is a drug.

Ephedra has been in the world food supply for thousands of years. There is ample support for adequate warnings on Ephedra Supplements but, like peanuts, a complete ban or lengthy front panel warnings are simply not necessary.

VIII. Conclusion

For the foregoing reasons, NVE Pharmaceuticals respectfully submits that FDA should adopt the warnings as proposed herein and cease and desist from its unwarranted calls for increased authority through the amendment or revocation of DSHEA. NVE Pharmaceuticals further submits that FDA already possesses a vast array of enforcement powers under the FDCA as presently enacted, and should utilize those powers rather than continuing to play politics at the expense of the public health.

Respectfully submitted,

ULLMAN, SHAPIRO & ULLMAN, LLP

on behalf of NVE PHARMACEUTICALS

ULLMAN, SHAPIRO & ULLMAN, LLP

COUNSELORS AT LAW

299 BROADWAY, SUITE 1700
NEW YORK, NY 10007

TEL. (212) 571-0068

FAX. (212) 571-9424

www.usulaw.com

usu@usulaw.com

ROBERT ULLMAN
STEVEN SHAPIRO*
MARC S. ULLMAN

SETH A. FLAUM*^o

TRADEMARK COUNSEL
DENNIS H. CAVANAUGH

BUSINESS & TECHNOLOGY COUNSEL
IRA R. HECHT*^{Δ†}

OF COUNSEL
IRVING L. WIESEN

* ADMITTED IN NY & NJ
o ADMITTED IN MD & DC
Δ ADMITTED IN FL
† CPA

WASHINGTON AFFILIATE
JAMES M. JOHNSTONE
1776 K STREET, NW
WASHINGTON, DC 20006

LONDON AFFILIATES
WEDLAKE BELL
16 BEDFORD STREET
COVENT GARDEN
LONDON WC2E 9HF
ENGLAND

E. U. CORRESPONDENT
LAFILL VAN CROMBRUGGHE
& PARTNERS
VOSSENDREEF 6 BUS 1
B-1180 BRUSSELS,
BELGIUM

April 1, 2003

VIA FACSIMILE (202) 225-4099 & FEDERAL EXPRESS

The Honorable Henry A. Waxman
2204 Rayburn House Office Building
Washington, D.C. 20515

Dear Rep. Waxman:

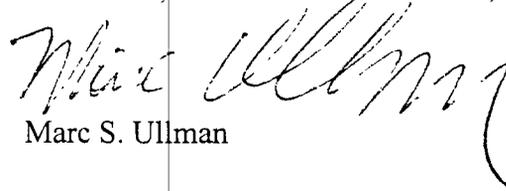
This morning I had occasion to attend your keynote presentation to the annual conference of the Food and Drug Law Institute. I found your comment on the need for honest, scientific based regulation particularly relevant and significant.

During your presentation, you stated that the Food and Drug Administration ("FDA") is in possession of evidence demonstrating that 100 deaths were "probably caused" by ephedra. This statement appears to conflict with the conclusions of the RAND Corporation's study of ephedra,¹ which reports that a comprehensive review of the public literature and all evidence in the possession of FDA revealed only two fatal "sentinel events" involving ephedra.²

In light of the important legal, regulatory and policy issues involving ephedra, I respectfully submit that it is extremely important for you to identify the additional 98 cases where ephedra "probably caused" fatal adverse events. Because FDA is presently in the process of promulgating regulations governing the sale of ephedra products, I urge you to release this information immediately. Such action will help ensure that the final regulations will be both honest and science based.

Respectfully yours,

ULLMAN, SHAPIRO & ULLMAN, LLP



Marc S. Ullman

¹ The Rand Report, entitled "Ephedra and Ephedrine for Weight Loss and Athletic Performance Enhancement: Clinical Efficacy and Side Effects," was commissioned by the National Institute of Health to review evidence on the risks and benefits of ephedra and ephedrine. It was prepared for the U.S. Department of Health and Human Services and was released by FDA on February 28, 2003.

² Rand notes that the classification of a "sentinel event" does not imply a proven cause and effect relationship between the ephedra supplement and the adverse event, p. 89.