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April 17, 1998

VIA HAND

Dockets Management Branch (HFA-305)  
Food and Drug Administration  
12410 Parklawn Drive  
Room 1-23  
Rockville, MD 20857

Re: Docket No. 98N-0148

(Notice requesting Data or Comments regarding Dihydroetorphine, Ephedrine, or Remifentanil)

Dear Madam or Sir:

This comment is being submitted on behalf of Weider Nutrition International, Inc. ("Weider"). A Utah corporation, Weider is one of the largest suppliers of health, fitness and wellness products in the world. Weider manufactures and markets products in the sports nutrition, bottled drink, diet, natural vitamin and nutritionally based snack bar categories, including some supplements that contain ephedrine alkaloids. Weider has been a health, fitness and sports nutrition leader for nearly fifty years since its founding in 1939.

In a Notice published by the FDA on March 18, 1998, the agency requested information concerning the potential abuse, medical usefulness and/or trafficking of three substances. In that notice the FDA announced that the information would be used to prepare a response to be submitted to the World Health Organization ("WHO"). Weider understands that WHO will use the information it receives to determine whether it should recommend that certain international restrictions be placed on Dihydroetorphine, Ephedrine, or Remifentanil.

Weider is limiting its comments to the submission of information on the highly varied international uses and benefits of ephedrine. Weider supports the FDA's position that ephedrine need not be regulated as a controlled substance and that, indeed, it may be -- and has been -- successfully regulated as a food (when consumed as a natural constituent of ephedra and ephedra-based teas), as a dietary supplement, and as an OTC

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drug--depending on its intended use. Although ephedrine, like many other ingredients, such as caffeine, may be abused, regulating its safe use does not *require* international controls. Rather each nation -- faced with its own unique history of ephedrine use and regulation -- is equipped with means both necessary and sufficient to address the unique problems encountered through national patterns of use and abuse. A "one size fits all" approach will unnecessarily restrict ephedrine use and ephedrine commerce in countries that benefit from ephedrine. Whether ephedrine is classified as an OTC drug, a prescription drug, a dietary supplement, or a food depends on the unique regulatory construct of the country in which it is sold. For example, in Canada, ephedrine is regulated as a traditional herbal medicine (THM), while in England, ephedrine is sold by prescription only. In China, Japan and France, synthetic ephedrine products are regulated as OTCs. In Asian countries, naturally occurring ephedrine is available in herbal shops. Due to diverse uses and systems of regulation throughout the world, it would be inappropriate to regulate ephedrine under one uniform standard. Indeed, such a standard would upset and replace national regulatory systems that are both necessary and sufficient to meet the peculiar needs of each country.

In these comments, Weider submits information on the historically and culturally diverse uses of ephedrine and on the scientific evidence that substantiates ephedrine's medicinal and nutritional benefits and safe use.

## **I. The Inadvisability of WHO Adopting a Uniform International Regulation for Ephedrine**

Ephedra, also known as ma-huang, is a small shrub. There are 40 species of the plant. They occur naturally worldwide in Asia, North America, South America and Europe. The ephedra plant can be found in all four of the southwestern deserts of the United States. It is indigenous to northwest India, Pakistan, and China. Ephedra has been used for thousands of years, primarily in China and India, and has a history of safe use there and in North America when consumed in moderation as foods, dietary supplements, or medicinal herbs. The use of ephedrine, or ma-huang, has been traced back as far as 3000 B.C. In ancient China it was used as a medical agent by Chinese physicians who prescribed it for various respiratory conditions such as colds, asthma and hay fever.<sup>1</sup>

Ephedrine has also been traditionally used in the United States. Ephedra is cultivated in the dry regions of North America and is consumed as "Mormon Tea" or "Squaw Tea." In 1847 when the Mormons arrived in Utah, the native Indians introduced them to ephedrine. The Mormons used it as a substitute for coffee and black tea and to treat medical conditions such as asthma and hay fever. Ephedrine was also used to make bread. The history reflects no safety problems arising from consumption of ephedrine in teas and foods.<sup>2</sup>

Ephedra has been used in different cultures in different ways: as a healing herb, as a food ingredient, as a food, as a tea, and as a beverage. As a healing herb, ephedra

serves as a nasal decongestant, a central nervous system stimulant, and a treatment for bronchial asthma.<sup>3</sup>

While ephedra is widely used as a healing herb, it is also considered a food in several regions of the world. For example in India, the berry from the ephedra shrub is consumed as a fruit. Also certain tribes from the Himalayas use the ephedra berry as a food source. Among desert plants, the ephedra species is extremely high in Vitamin C which makes it a major contributor to vitamin requirements of humans subsisting on the local food-flora.<sup>4</sup>

Each country has its own unique pattern of ephedrine use and abuse. Each country has its own unique safety record. Each country's people have their own peculiar reliance upon ephedrine. In some countries ephedrine (the berry from the ephedra shrub) is a food source important to human survival and welfare. In other countries it is an important food additive in baked goods, including breads. In other countries it is consumed as a tea or other beverage. In still others, it is available as a dietary supplement, herbal remedy, or OTC drug. Relied upon for widely varying purposes that range from sustenance to nasal decongestion, ephedrine has great importance around the world. Uniform categorization of ephedrine as a controlled substance is, thus, inappropriate.

Any restriction such a classification would impose on a safe national use could have profoundly adverse consequences. International regulation could deprive people in different societies of important food sources, nutritional supplements, or herbal remedies. Those least able to afford substitutes, the large populations of poor who live in India, China, and other African and Asian countries, would suffer the most. WHO would do well to trust the expertise of each country's health regulators to determine how best to govern appropriate domestic uses of this multifaceted substance. In light of the extraordinary diversity in experience, history, and culture affecting ephedra use, solutions to problems of abuse must be tailored to the differing needs of each country and must not be subject to any uniform international strictures.

## **II. U.S. Regulation of Ephedrine**

The FDA under the Food Drug and Cosmetic Act ("FDCA") regulates the safe use of ephedrine as over-the-counter (OTC) drug products and, under the Dietary Supplement Health and Education Act ("DHSEA"), as dietary supplements. Under the FDCA, a drug is permitted for OTC sale and use by the public, unless, because of its toxicity or other potential for harmful effect or because of the method of collateral measures necessary for its use, it may be safely sold only under the supervision of a licensed practitioner. 21 CFR § 330.10(a)(4)(vi). A product preparation that meets the standards of an applicable OTC monograph and the conditions set forth in 21 CFR § 330.1 is generally recognized as safe and effective and can be marketed as an OTC product. 21 CFR § 330.1.

On October 2, 1986, the FDA published a final OTC monograph providing for the use of ephedrine as an active ingredient in bronchodilators. 51 Fed. Reg. 35339 (1986) (codified at 21 CFR § 341.16). In that monograph the FDA approved ephedrine, ephedrine hydrochloride, ephedrine sulfate, epinephrine, epinephrine bitartrate, ractephrine hydrochloride and ractephrine hydrochloride as safe and effective active ingredients in OTC bronchodilators. 21 CFR § 341.16.

On August 23, 1994, the FDA published a final monograph providing for the use of ephedrine as an active ingredient in nasal decongestant products. 59 Fed. Reg. 43409 (1994) (codified at 21 CFR § 341.20). In that monograph the FDA approved ephedrine, ephedrine hydrochloride, and ephedrine sulfate as safe and effective active ingredients in OTC topical nasal decongestant products.

Recently, the U.S. has been faced with a surge of illicit use of methamphetamine. In investigating methods of controlling that problem, ephedrine has been identified as a precursor substance used in synthesizing methamphetamine and methcathinone. In response to the problem, the Drug Enforcement Administration ("DEA") has requested that ephedrine and its derivatives be subject to certain controls. In response to that request, on July 27, 1995, the FDA published a proposed rulemaking, proposing to remove ephedrine and its derivatives from the OTC active ingredient list and to classify them as not generally recognized as safe. To date, the FDA has not finalized those proposals.

Ephedrine is used as an ingredient in OTC drugs and as a dietary ingredient in dietary supplements. Dietary supplements and their ingredients are governed by the Dietary Supplement Health and Education Act ("DSHEA"). Under DSHEA an ingredient may be included in a dietary supplement provided that its use has not been banned and the manufacturer has determined that its inclusion is safe. Recently, the FDA has expressed some concern regarding the amount of ephedrine that should be included in dietary supplements. Dietary supplements that contain ephedrine and ephedrine alkaloids are sold widely throughout the United States. Since 1993, the FDA has received more than 800 adverse incident reports concerning products that contained, or were believed to contain, ephedrine. In response to those reports, on June 4, 1997, the FDA published a proposed rule in the Federal Register to regulate the presence of ephedrine in dietary supplements. 62 Fed. Reg. 30678. The agency has not yet promulgated a final rule but has received numerous comments supporting a typical dosage limit of 150 mgs in divided doses in accordance with the peer-reviewed scientific literature.

Although the United States' regulatory regime accounts for many varieties of use of ephedrine products (as foods, dietary supplements, and drugs), neither the U.S. system nor any other single regulatory regime (such as that proposed by WHO) should supplant each nation's own response to its unique experiences with this multifaceted product.

### **III. Science on Ephedrine Safety and Use<sup>1</sup>**

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<sup>1</sup> All scientific studies referenced in this section are attached.

WHO is seeking information on ephedrine to determine whether it should be regulated internationally as a controlled substance. As part of that determination, WHO requested information on the medicinal usefulness of ephedrine. In the United States substances are usually regulated as controlled substances where there is evidence of pharmacological effects, a pattern of abuse, a significant risk to public health and evidence of physiological or psychological dependence. 21 U.S.C. §811(c). The scientific studies conducted on ephedrine do not demonstrate that ephedrine functions as a controlled substance. To the contrary, scientific studies demonstrate that ephedrine is safe, and comparable to caffeine in its effects.<sup>5</sup>

Research on obesity indicates that obese individuals possess a decreased post-prandial thermic response.<sup>6</sup> Whether the decrease in the metabolic rate or thermic response is a cause or a consequence of obesity remains to be determined. Numerous studies suggest that ephedrine has thermogenic properties that assist weight reduction when combined with a low calorie diet and increased exercise.<sup>7</sup> Research over the past two decades has further substantiated the effectiveness of ephedrine in producing weight loss, particularly when it is combined with other xanthines, such as caffeine and aspirin. When used under normal conditions in doses of 60 mg to 150 mg per day, ephedrine produces minimal side effects.<sup>8</sup> Moreover, the side effects resulting from the use of ephedrine are strikingly similar to those side effects experienced by caffeine users. For example, a study conducted by Astrup et al. demonstrated that the reported side effects of caffeine, including palpitations, headaches, dry mouth, restlessness, and dizziness were comparable to the side effects reported by users of ephedrine.<sup>9</sup>

In the segment that follows Weider identifies a sample of the many studies that have been conducted on the usefulness, safety and efficacy of ephedrine. The studies demonstrate that ephedrine has many beneficial characteristics and minimal side effects.

### ***Ephedrine and Caffeine Combinations Reduce Weight of Obese Subjects***

Since the 1970's, obesity researchers have found that the combination of ephedrine and caffeine is particularly effective in reducing the weight of obese subjects (with minimal side effects). Research over the past decade reveals that the thermogenic properties of ephedrine generate weight loss in diet-restricted obese patients. In particular, the studies of Astrup, et al. demonstrate that the synergistic interaction between combinations of ephedrine and caffeine on weight loss provide a safe drug combination with the necessary thermogenic properties to assist in the management of obesity.

In a 1992 study conducted by researchers Astrup and Toubro, the safety and efficacy of ephedrine and caffeine, alone and in combination, were tested in 141 obese adults.<sup>10</sup> The double blind study, conducted over a period of twenty-four weeks, indicated that ephedrine in combination with caffeine is more effective than placebo, ephedrine alone, or caffeine alone in promoting weight loss in obese adults. The ephedrine/caffeine combination caused subjects to experience increased energy and decreased appetite. Although some subjects receiving the ephedrine/caffeine compound

experienced vertigo, nervousness, and insomnia, the side effects were benign and disappeared after eight weeks.

The researchers extended the experiment from twenty-four weeks to fifty weeks to determine the effects of ephedrine and caffeine over a longer period of time.<sup>11</sup> Ninety-nine of the previous study's 141 subjects were given ephedrine and caffeine alone and in combination. The results of the long-term study supported the findings of the earlier study that the ephedrine/caffeine combination is more effective than placebo, caffeine, or ephedrine at promoting and maintaining weight loss for obese adults. In addition, researchers found that the incidence of side effects did not increase with long term use. Measurements and examination of the patients receiving the combined ephedrine/caffeine combination also confirmed the protein sparing effect of ephedrine. The results revealed that the ephedrine/caffeine mixture maintains lean body mass while increasing fat loss.

In 1993, researchers Astrup and Toubro again tested the efficacy of caffeine and ephedrine, alone and in combination, on six healthy adults.<sup>12</sup> The subjects' responses to the compounds affirmed that the combination of ephedrine and caffeine produced heightened thermogenic and metabolic effects. The double blind placebo-controlled study measured eleven different physiologic parameters after the subjects received ephedrine, caffeine, combined ephedrine and caffeine, or a placebo. The thermogenic and metabolic responses were greatest in the subjects treated with the ephedrine and caffeine combinations. Although the subjects receiving ephedrine experienced side effects, including slight increases in blood pressure and heart rate, the side effects that occurred from taking ephedrine were similar to those experienced from using caffeine, a compound "Generally Recognized as Safe" by the FDA and consumed widely in virtually every country in the world.

In 1994, Buemann, et al., studied the effect of ephedrine and caffeine on plasma lipids and lipoproteins.<sup>13</sup> The researchers studied forty-one obese women in a double-blind placebo study. While the treatment group received an ephedrine and caffeine combination and a restricted diet, the control group received a placebo and the same restricted diet. Although the eight-week study did not produce significant differences in weight loss between the two groups, the subjects did not experience significant side effects either. Additionally, the subjects who received the ephedrine-caffeine compound exhibited a significantly lower triglyceride level. Other changes in HDL ratios indicated that ephedrine may have beneficial effects on lowering plasma lipid levels while supporting a low calorie weight reduction diet.

Researchers Horton and Geissler conducted a study in 1995 that revealed that the combination of ephedrine and caffeine increased the metabolic rate of thirty adults.<sup>14</sup> The researchers observed the effect of ephedrine on three groups of adults: lean adults who did not restrict caloric intake; adults overweight by up to 11.8% who did restrict their caloric intake; and adults overweight by at least 20%. The researchers measured the subjects' responses between one and 160 minutes after ingesting a liquid meal mixture. Ephedrine was combined in a liquid meal in dosages similar to those found in over-the-counter ephedrine preparations. The liquid meal with ephedrine and caffeine had a greater effect on raising the metabolic rate than meal alone, liquid meal with ephedrine

alone, or liquid meal with ephedrine and aspirin. The effect was most notable in the obese subjects as indicated by increased post-prandial thermogenesis. The study indicated that in the short term a one time dose of liquid meal with caffeine and ephedrine potentates the increased metabolism effects of ephedrine in obese patients.

### ***Ephedrine Reduces Weight of Obese Subjects with Minimal Side Effects***

Researchers have also studied the effects of ephedrine without the use of caffeine. These studies indicate that ephedrine reduces weight more effectively when combined with caffeine and/or aspirin. The studies also indicate that subjects taking ephedrine experience minimal side effects and occasional weight loss.

In 1987, researchers Pasquali, et al. observed the effects of 150 mg of ephedrine on five obese females.<sup>15</sup> Previously resistant to weight loss on low-caloric diets, the subjects took ephedrine daily for one month. The researchers administered a placebo to a control group of five obese women who had also previously been resistant to weight loss on low-caloric diets. Although both groups consumed a low calorie diet during the observation period, the women who received ephedrine lost significantly more weight than the women who received the placebo. Moreover, neither group experienced significant adverse effects from consuming ephedrine.

In 1992, Pasquali, et al. observed the effects of ephedrine on the protein metabolism and resting metabolic rate (RMR) of obese subjects.<sup>16</sup> In that double blind placebo study researchers administered 50 mg of ephedrine to ten obese adults three times a day over a period of two weeks. The subjects who received ephedrine experienced a significant protein sparing effect and did not exhibit a reduced RMR. The ephedrine group had lower nitrogen excretion and improved nitrogen balances. The ephedrine group had a higher protein accumulation without the level of muscle protein breakdown that the control group experienced. The apparent protein sparing effect of ephedrine is valuable in preventing the negative nitrogen balances that often accompany low-calorie diets. The study affirmed ephedrine's ability to maintain the RMR.

Numerous studies reveal that the ingestion of ephedrine produces minimal side effects.<sup>17</sup> White, et al. observed the effects of ephedrine as it occurs in the herb ma-huang on the blood pressures and heart rates of twelve healthy adults. These effects were measured against effects of known doses of ephedrine and pseudoephedrine caplets. There was a slower absorption rate of prepared ephedrine by subjects who had previously ingested ma-huang during the observation period. All other physiologic effects (blood pressure changes, heart rate changes) were so variable as to be inconclusive. However, the subjects experienced no adverse effects from the preparations, including those who received all of the preparations.

As the scientific studies indicate, the effects associated with the use of ephedrine are not those normally associated with a controlled substance. Indeed, none of the studies indicated that ephedrine produced pharmacological effects normally associated with the use of controlled substances. In fact, the science indicates that the side effects of ephedrine are the same or similar to those associated with caffeine.<sup>18</sup> Accordingly,

ephedrine need not be regulated as a controlled substance. Instead, lesser controls, tailored to individual patterns of use, can be enacted to ensure that ephedrine is not abused.

#### **IV. Conclusion**

The scientific studies demonstrate that ephedrine does not function as a controlled substance. It is not inherently unsafe, and the scientific evidence demonstrates it produces effects virtually identical to those commonly experienced from caffeine ingestion. The scientific studies reveal that ephedrine facilitates weight loss and provides other medicinal and nutritional benefits.

International regulation of ephedrine as a controlled substance would be counterproductive. It would usurp each country's long-standing independent regulatory regime that provides a tailored, necessary, and sufficient response to meet the history of ephedrine use and abuse unique to each country. Such usurpation would deprive a large portion of the world's population of a useful source of food, food supplementation, and medicine. The impact would be most deleterious upon poorer peoples of the world who now look to ephedrine as an important food source and herbal remedy.

In light of the scientific evidence in support of ephedrine's safety and efficacy and the great diversity in world use of ephedrine, Weider strongly supports FDA's position that WHO should not categorize ephedrine as a controlled substance.

Respectfully submitted,



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- <sup>1</sup> Michael Stuart, *The Encyclopedia of Herbs and Herbalism* (1979).
- <sup>2</sup> Jane Rose, *Herbs and Things* (1972).
- <sup>3</sup> Varro E. Tyler, *The Honest Herbal - A Sensible Guide to the Use of Herbs and Related Remedies* (1993); M.B. Krieg, *Green Medicine* (1964).
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