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VIA HAND-DELIVERY

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

Re. Docket 95N-0304: Dietary Supplements Containing Ephedrine Alkaloids

Dear Sir or Madam:

On behalf of our client, Metabolife International, Inc. ("Metabolife"), we are hereby submitting these comments to the docket recently reopened by the Food and Drug Administration ("FDA" or "Agency") to address regulatory and scientific issues associated with dietary supplements that contain ephedrine alkaloids. Metabolife has enclosed with this submission many scientific studies that to its knowledge may not have been previously introduced into any of FDA's ephedra-related administrative dockets. These studies support the safety and efficacy of dietary supplements that contain ephedrine alkaloids.

As the Agency is aware, the RAND Corporation ("RAND") recently completed a review of scientific and anecdotal information associated with ephedrine alkaloids, and concluded that dietary supplements that contain ephedrine alkaloids have proven benefits for weight loss purposes.[1] Moreover, RAND concluded that dietary supplements that contain ephedrine alkaloids produce weight loss benefits of up to 2 pounds per month, for up to 6 months[2] (longer

[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, "RAND Report").

[2] RAND Report, pp. vi, 219.

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than the period of time recommended by FDA's own advisory committee to demonstrate product efficacy for weight-loss OTC drug products under the OTC Drug Review[3]).

From a safety perspective, RAND acknowledged that the strongest evidence of causality comes from clinical trials,[4] and noted that no serious adverse events (death, myocardial infarction, stroke etc.) were reported in the 52 clinical trials that RAND reviewed.[5] With regard to anecdotal events, RAND acknowledged that case reports and "sentinel events" do not prove a cause-and-effect relationship.[6] The problems associated with the use of anecdotal data for causation analysis are well known to FDA. Based upon the estimated millions of people who use dietary supplements that contain ephedrine alkaloids, there is no scientific rationale to conclude that such products cause serious adverse events when used in accordance with product labeling.

As explained herein, based upon an analysis of the scientific data and information associated with ephedrine alkaloids, and the longstanding marketing of OTC drug products that contain ephedrine alkaloids, we believe the proven weight loss benefits of such products clearly outweigh any hypothetical serious risks. Products with proven weight loss benefits, and only hypothetical serious risks, do not present a significant or unreasonable risk of illness or injury under conditions of use recommended in product labeling.

It should be emphasized, however, that Metabolife has long sought science-based regulation of dietary supplements that contain ephedrine alkaloids. Such products are not for everyone, and consumers are directed to consult with a physician prior to use if they have specific preexisting conditions. Accordingly, Metabolife will not oppose final adoption of the proposed warning label developed by the Agency.[7]

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[3] 47 Fed.Reg. 8466, 8482 (1982) (deciding "that a study of 12 weeks' duration would satisfy the Panel's goal").

[4] RAND Report Summary, p. 6.

[5] RAND Report Summary, p. 4; RAND Report, p. 221.

[6] RAND Report Summary, p. 6.

[7] By indicating that Metabolife will not oppose the final adoption of the warning label proposed by the Agency, Metabolife makes no admission of fact regarding FDA's rationale for such a warning or the validity of relying upon anecdotal data to make science-based decisions. Based upon its review of the science, Metabolife believes FDA should at least consider finalizing a warning that expressly indicates that although side effects have been reported in temporal association with ingestion of ephedrine alkaloids, it is not possible to conclude that such events were caused by such ingestion. In this regard, FDA may want to consider using as a template language contained in the official drug labeling for Viagra® - which provides: "Serious cardiovascular events ... have been reported post-

Executive Overview

In its recent Federal Register notice, the Agency requested comments in response to four issues: (1) FDA's proposed mandatory warning statement; (2) new "evidence" on health risks claimed to be related to ephedra; (3) whether the currently available scientific evidence and medical literature present a "significant or unreasonable risk of illness or injury under conditions of use recommended or suggested in labeling" from dietary supplements containing ephedra; and (4) whether additional legislative authorities, if any, would be necessary or appropriate to enable FDA to address this issue more effectively.[8]

With regard to the first question, Metabolife will not oppose final adoption of FDA's proposed mandatory warning statement. When formulating the final label, however, FDA should take into consideration the fact that a warning label similar if not identical to the one included on the label of Metabolife 356® recently obtained a favorable review in a report issued by the Department of Health and Human Services, Office of Inspector General.[9] With regard to the ephedra warning label, that report provides:

> Our interviewees tended to prefer warnings that mentioned specific medical conditions and that were written in simple language. For example, most people liked the Ephedra warning because of its completeness. It addresses topics such as contraindications, interactions, maximum dosage, and adverse effects.[10]

For years, Metabolife, and responsible members of the dietary supplement industry, have supported strong warning statements for dietary supplements that contain ephedrine alkaloids – along with even more comprehensive regulation of such products. Specifically, Metabolife has long been at the forefront in supporting science-based Federal and state regulation or legislation

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marketing in temporal association with the use of Viagra®.... It is not possible to determine whether these events are related directly to Viagra®, to sexual activity, to the patient's underlying cardiovascular disease, to a combination of these factors, or to other factors." *See* Physicians' Desk Reference 2656 (Thomson PDR, 57th ed. 2003) (*See* Attachment 1).

[8] 68 Fed. Reg. 10417 (2003).

[9] Department of Health and Human Services, Office of Inspector General, "Dietary Supplement Labels: Key Elements" (March 2003) (hereinafter, "OIG Report- Dietary Supplement Labels"). (*See* Attachment 2).

[10] OIG Report – Dietary Supplement Labels, p. 11.

(such as the state statutes enacted in Ohio, Washington, Hawaii, Nebraska and Michigan) that would include:

- Dosage limits of no more than 25 mg of ephedrine alkaloids per product serving, and no more than 100 mg per day.

- Strict warning labels, including warnings to consult a physician if the individual has pre-existing medical conditions.

- Prohibition on claims that the product may be useful to achieve an altered state of consciousness, euphoria, or as a "legal" alternative for an illicit drug.

- Prohibition on sale to minors.

- Ban on the use of synthetic ephedrine alkaloids in dietary supplements.

- Mandatory batch testing to ensure that products contain the amount of ephedrine alkaloids that they are claimed to contain.

Metabolife continues to support the above initiatives.

With regard to the latter three questions posed in FDA's Federal Register notice,[11] Metabolife's position is equally clear: (1) the four new studies cited by the FDA in its Federal Register notice as "new evidence" are a hodgepodge of inconclusive analyses that do not impact the favorable scientific assessment of ephedrine alkaloids; (2) dietary supplements that contain ephedrine alkaloids do not present an "unreasonable risk" – based upon the extensive scientific support for such products; and (3) FDA has sufficient authority under the Dietary Supplement Health and Education Act of 1994[12] ("DSHEA") to regulate dietary supplements, and new legislation is not needed.

As explained herein, FDA is obligated to conduct a risk/benefit analysis to determine whether dietary supplements that contain ephedrine alkaloids pose a "significant or unreasonable risk of illness or injury under conditions of use recommended or suggested in labeling." In this case, as demonstrated by government-sponsored research and analyses, the evidence is clear - ephedra is effective in producing weight loss of up to two pounds per month, and serious risks associated

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[11] 68 Fed. Reg. 10417 (2003).

[12] Dietary Supplement Health and Education Act of 1994 ("DSHEA"), Pub. L. No. 103-417, 108 Stat. 4325 (1994).

with the product are unproven and hypothetical. Based upon these scientific facts, it is quite obvious that ephedra does not pose a significant or unreasonable risk of illness or injury.

In conducting its risk/benefit assessment, it is imperative that the Agency acknowledge the following:

* The Congressionally mandated statutory standard under DSHEA requires FDA to evaluate dietary supplements based upon product labeling in order to determine if they present a significant or unreasonable risk to consumers. Congress recognized that adults are capable of reading labeling instructions, and therefore products should not be subject to challenge based upon potential consumer abuse or misuse.

* FDA has repeatedly acknowledged, including in comments to the Office of Management and Budget ("OMB"), that its regulations must be "science-based." FDA has repeatedly indicated that well-controlled clinical trials are the best type of scientific data – and anecdotal data (case reports) are insufficient for most scientific purposes.

* The "unreasonable risk" standard has been applied and interpreted by the judiciary in a variety of contexts, and courts agree that the standard requires an agency to provide a very high level of scientific evidence in support of its conclusions.

* Reportedly, some 40% of all Americans are over-weight, potentially leading to serious health problems. Many Americans need over-the-counter support to help them achieve their weight loss objectives and/or to help them maintain their weight.

* RAND just completed a review of the applicable science and anecdotal information associated with ephedrine alkaloids, not including four new inconclusive analyses referenced in FDA's Federal Register notice.

* With regard to efficacy, RAND concluded that upon review of numerous clinical studies (over twenty), the evidence supports the efficacy of ephedrine, ephedrine plus caffeine, or dietary supplements that contain ephedra, for weight loss purposes over a six-month period (three months longer than the weight loss study recommended by FDA's own Advisory Review Panel under the OTC Drug Review) – resulting in weight loss of two pounds per month more than placebo.

Adding caffeine to ephedrine "is associated with a statistically significant increase in short-term weight loss."[13]

* With regard to safety, FDA, RAND, and the National Institutes of Health, National Advisory Council for Complementary and Alternative Medicine (NACCAM) Working Group on Ephedra ("NIH Working Group"), have all indicated that there is no scientific support to conclude that ephedra causes serious adverse events.

* In FDA's recently published White Paper on Ephedra, entitled: "Evidence On The Safety And Effectiveness Of Ephedra: Implications For Regulation," FDA acknowledged that a review of all of the information does "not establish definitive causal evidence of a statistically significant elevated risk of death or serious injury from ephedra."[14]

* The White Paper also provides: "Thus, as has marked the history of inquiries into ephedra's safety, further analysis of safety risks involves case reports - the weakest form of epidemiological evidence since there are no direct 'controls' for any confounding factors or even for the natural occurrence rate of these serious events."

* In the same White Paper, FDA acknowledged that there is no "smoking gun" that proves a causal relationship between ephedra and serious adverse events.

* RAND concluded that no serious adverse events (e.g. death, myocardial infarction, stroke, etc.) were reported in 52 clinical trials that were reviewed.

* RAND indicated that the most important limitation in its analysis is that an assessment of case reports is insufficient to reach conclusions regarding causality.

* RAND acknowledged that the strongest evidence of causality should come from clinical trials. Moreover, RAND "could not determine definite causality from case reports."

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[13] RAND Report, p. 219.

[14] *Evidence On The Safety And Effectiveness Of Ephedra: Implications For Regulation*, FDA White Paper on Ephedra, *available at* www. fda.gov/bbs/topics/NEWS/ephedra/whitepaper.html (hereinafter, "White Paper").

* RAND acknowledged that scientific studies (not additional case reports) are necessary in order to assess the possible association between consumption of ephedra-containing dietary supplements and serious adverse events.

* In a June 14, 2002, letter to Sidney Wolfe, based upon the information available to him at the time, Secretary Thompson of HHS indicated that the "FDA has advised [him] that the types of observed outcomes reported in relationship to the ingestion of ephedrine alkaloids are not uncommon in the general population and therefore the reports alone do not provide a scientific basis for assessing the safety of ephedrine alkaloids or establish a link between the reported events and the ingestion of ephedrine alkaloids."[15]

* On February 26, 2003, the NIH Working Group recently evaluated the RAND Report, and concluded that the data on ephedra safety is inconclusive – it cannot be demonstrated, based upon current data and information, that ephedra is not safe.[16] On March 17, 2003, the NIH Working Group suggested initiation of a multi-site, prospective case-control study to assess the risk associated with taking ephedra.[17] The NIH Working Group estimates that the proposed study would take 4-8 years, and cost $2-4 million per year.

* The four new "studies" cited in FDA's Federal Register notice constitute a hodgepodge of inconclusive analyses that, as explained below, fail to meet the scientific criteria used by RAND to evaluate ephedra-related clinical studies. See Section II, infra.

* FDA is obligated to consider the long-standing marketing, and favorable safety profile, of drug products that contain ephedrine alkaloids under the OTC Drug Review. Such products provide more ephedrine on a daily basis than dietary

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[15] Letter from Health and Human Services to Sidney Wolfe (June 14, 2002) (hereinafter, "HHS Letter"). (*See* Attachment 3).

[16] See National Advisory Council for Complementary and Alternative Medicine (NACCAM) Working Group on Ephedra, Report of the Ephedra Working Group, presented March 17, 2003, appears at http://nccam.nih.gov/health/alerts/ephedra/working-group.pdf. (*See* Attachment 4).

[17] National Advisory Council for Complementary and Alternative Medicine (NACCAM) Working Group on Ephedra, Project Concept Review, Case-Control Study to Investigate the Safety of Ephedra March 17, 2003, *available at* http://nccam.nih.gov/research/concepts/consider/ephedra.htm. (*See* Attachment 5).

supplements that contain ephedra, and are routinely ingested along with caffeine. FDA has concluded that such products are "generally recognized as safe and effective" for their intended use. Moreover, these bronchodilator products containing ephedrine do not contain any duration of use limitation. It is unclear what scientific support FDA relies upon in order to theorize that a lower level of ephedrine provided in dietary supplement products may pose a risk to health while it does not do so for OTC bronchodilator drugs.

I. Scientific Information In Support of the Safety and Efficacy of Dietary Supplements that Contain Ephedrine Alkaloids

Metabolife has identified a number of studies that, to our knowledge, may not have been included in FDA's docket regarding dietary supplements that contain ephedrine alkaloids.[18] Some of the studies identified by Metabolife include subjects who ingested ephedrine alkaloids for a year or longer. A list of these studies is provided below.

A. Studies Less than Six Months in Length

1. Fifty-Six Ephedrine Studies.

A generally overlooked source of safety data is the older literature on clinical trials of ephedrine, many of which relate to the treatment of asthma and many of which also assess the combination of ephedrine with caffeine. A leading cardiac pathologist, Steven B. Karch, M.D., recently identified 56 of such studies that he reports include over 1000 individuals and support the safety and efficacy of dietary supplements that contain ephedrine alkaloids. All 56 studies, along with an overview chart prepared by Dr. Karch, are attached (*See* Attachment 6).

2. De Matteis, R., *Immunohistochemical identification of the β3-adrenoceptor in intact human adipocytes and ventricular myocardium: effect of obesity and treatment with ephedrine and caffeine*, 26 International Journal of Obesity 1442-1450 (2002). (*See* Attachment 7).

[18] Although the 56 studies identified by Dr. Karch may have previously been submitted to one of the ephedra-related dockets, we are ensuring FDA review by submitting all of the studies to the docket at the present time. (*See* Attachment 6). Some of these studies may also be addressed separately in this document.

3. Raum, W., *et al., Quality and quantity of surgically induced weight loss for morbid obesity improved by treatment with ephedrine*, 8 (Supp. 1) Obesity Research 55S (Oct. 2000). (*See* Attachment 8).

4. Kalman, D., *An acute clinical trial evaluating the cardiovascular effects of an herbal ephedra-caffeine weight loss product in healthy overweight adults*, 26(10) International Journal of Obesity Related Metabolic Disorders 1363-6 (2002). (*See* Attachment 9).

5. Kalman, D-S, *et al., Effects of a weight loss aid in healthy overweight adults: double-blind, placebo-controlled clinical trial*, 61(4) Current Therapeutic Research 199 (Apr. 2000). (*See* Attachment 10).

6. Armstrong, J., *The effect of commercial thermogenic weight loss supplement on body composition and energy expenditure in obese adults*, 4(2) Journal of Exercise Physiology (online) 28 (May 2001). (*See* Attachment 11).

7. Coffey, C. S., *et al., Safety of an herbal formulation including ephedra alkaloids dosed intermittently or continuously for weight control*, Unpublished, Conducted at the Department of Biostatistics, University of Alabama at Birmingham and Research Testing Laboratories, Great Neck, NY. (*See* Attachment 12).

B. Studies More than Six Months in Length

Despite the findings reported by RAND, there have been studies that have included subjects who have used ephedrine alkaloids for more than a six-month period. Although one of the studies was just conducted, two other studies were conducted ten years ago. The studies indicate that ephedrine and/or ephedrine in combination with caffeine is well tolerated and may be safely ingested on a long-term basis.

1. **Filozof, C., *et al., The effect of ephedrine plus caffeine after a 4-week portion-controlled diet*, 26(1) International Journal of Obesity S156 (2002). (*See* Attachment 13).**

The abstract for this study provides:

> The aim of the present investigation was to study the long-term effect on body weight, energy expenditure and plasma lipids of an ephedrine/caffeine combination after a 4-week portion-controlled diet. Twenty three patients (14 M/9 F, mean ± SD, age 44.8 ±, 9.ty, BMI: 36.6 ± 6.3 Kg/m^2) received a 900 kcal/day portion-controlled formula diet (PCFD) for 4 weeks. The subjects were then treated either with an ephedrine/caffeine combination (10/mg 100 mg) twice daily or placebo (P) for 11 months in a randomized, double blind study. During these months, the patients were given a low-fat (25 g), high carbohydrate diet and a lifestyle intervention involving nutritional education and increased physical activity. Height, weight, waist, body composition, energy expenditure, fasting plasma glucose and lipids were assessed at baseline, after the 4-week PCFD and at months 3 and 12. Body composition was measured by bioimpedance. Energy expenditure was assessed after a 10-h fast by indirect calorimetry. Mean weight loss during the first 4 weeks was 6.6 ± 4.0 Kg. Mean weight and weight loss in the E+C group was significantly higher then in the P group (7.3 vs. 2.4 Kg. and 11.9 vs. 5.5 cm, respectively). Mean resting metabolic rate (RMR) and respiratory quotient (RQ) decreased after the 4-week PCFD (mean ± SD, 1807.3 ± 206 to 1674.8 ± 187.6 kcal and 0.89 ± 0.005 to 0.79 + 0.02 $p < 0.001$). RMR and RQ were similar between groups at months 3 and 12. Plasma glucose, triglyceride and HDL-cholesterol concentrations decreases during the PCFD. No difference was found between groups in plasma glucose and lipid concentrations. Conclusions: Following a PCFD, C+E is effective in maintaining and improving weight loss for up to 1 year. The mechanism of action at these doses seems to be by reducing appetite. (Emphasis added.)

2. **Daly, P.A., *et al.*, *Ephedrine, caffeine and aspirin: safety and efficacy for treatment of human obesity*, 17 (Supp. 1) International Journal of Obesity S73 (1993). (*See* Attachment 14).**

The abstract for this study provides:

> The safety and efficacy of a mixture of ephedrine (75-150mg), caffeine (150mg) and aspirin (330mg), in divided premeal doses, were investigated in 24 obese humans (mean BMI 37.0) in a randomized double blind placebo-controlled trial. Energy intake was not restricted. Overall weight loss over 8 weeks was 2.2kg for ECA vs. 0.7 kg for placebo ($p < 0.05$). 8 of 13 placebo subjects returned 5 months later and received ECA in an unblinded crossover. After 8 weeks, mean weight loss with ECA was 3.2 kg vs 1.3 kg for placebo ($p = 0.036$). 6 subjects continued on ECA for 7 to 26 months. After 5 months on ECA, average weight loss in 5 of these was 5.2 kg compared to 0.03 kg gained during 5 months between studies with no intervention ($p = 0.03$). The sixth subject lost 66 kg over 13 months by self-imposed caloric restriction. In all studies, no significant changes in heart rate, blood pressure, blood glucose, insulin, and cholesterol levels, and no differences in the frequency of side effects were found. ECA in these doses is thus well tolerated in otherwise healthy obese subjects, and supports modest, sustained weight loss even without prescribed caloric restriction, and may be more effective in conjunction with restriction of energy intake.

3. **Toubro S., *et al.*, *Safety and efficacy of long-term treatment with ephedrine, caffeine and ephedrine/caffeine mixture*, 17 (Supp. 1) International Journal of Obesity and Related Metabolic Disorders S69 (1993). (*See* Attachment 15).**

The abstract for this study provides:

> In a randomized, placebo-controlled, double blind study, 180 obese patients were treated by diet (4.2 MJ/day) and either an ephedrine/caffeine combination (20mg/200mg), ephedrine (20mg), caffeine (200mg) or placebo 3 times a day for 24 weeks. 141 patients completed this part of the study. All medication was

> stopped between week 24-26 in order to catch any withdrawal symptoms. From week 26 to 50, 99 patients completed treatment with the ephedrine/caffeine compound in an open trial design, resulting in a statistically significant ($p = 0.02$) weight loss of 1.1kg. In another randomized, double-blind, placebo-controlled 8 week study on obese subjects we found the mentioned compound showed lean body mass conserving properties. We conclude that the ephedrine/caffeine combination is effective in improving and maintaining weight loss, further it has lean body mass saving properties. The side effects are minor and transient and no withdrawal symptoms have been found. (Emphasis added).

C. Studies Documenting the Benefits of Losing Weight

A number of recent studies have documented the significant health benefits of weight loss. A few of these studies are identified below:

1. **Kurth, T., *et al., Body mass index and the risk of stroke in men*, 162 Archives of Internal Medicine 2557-62 (2002). (*See* Attachment 16).**

2. **Kenchaiah, S., *et al., Obesity and the risk of heart failure*, 347(5) The New England Journal of Medicine 305 (Aug. 1, 2002). (*See* Attachment 17).**

3. **Gregg, E., *Intentional weight loss and death in overweight and obese U.S. adults 35 years of age and older*, 135(5) Annals of Internal Medicine 383-90 (2003). (*See* Attachment 18).**

II. The Analysis Conducted by RAND Supports the Safety and Efficacy of Ephedra

At the direction of several national funding agencies and in consultation with RAND's Technical Expert Panel, RAND addressed numerous research questions posed by the funding agencies regarding the safety and efficacy of herbal ephedra and ephedrine for weight loss and athletic performance.

In conducting the study, RAND undertook both a literature review and a synthesis of existing evidence, including a review of clinical trials, adverse event reports ("AERs") on file with the FDA, published case reports, and call records submitted by Metabolife to FDA. Specifically, through a search of published reports, journal articles, conference presentations, and various

sources of unpublished studies, RAND identified 52 controlled clinical trials of ephedrine or herbal ephedra for weight loss or athletic performance in humans. Additionally, FDA provided RAND with copies of adverse event reports related to herbal ephedra and to ephedrine, which in some cases included interviews with patients and/or family members, medical records, and copies of product labels. Finally, Metabolife made available call records for review.

To review efficacy, RAND abstracted data from reports of controlled trials onto a custom-designed form containing questions regarding a number of variables, including, among others, the number of patients, co-morbidities, dosage, and adverse events. Only trials of at least eight-weeks treatment duration were considered for a meta-analysis of weight loss efficacy. The effects of ephedra/ephedrine on weight loss were examined in six different types of comparisons: (1) ephedrine versus placebo; (2) ephedrine plus caffeine versus placebo; (3) ephedrine plus caffeine versus ephedrine; (4) ephedrine versus other active treatment; (5) ephedra versus placebo; and (6) ephedra plus herbs containing caffeine versus placebo. Studies on athletic performance were compared and contrasted in a narrative review rather than via statistical synthesis, due to the varied nature of the studies.

To review safety, RAND reviewed each report of a controlled trial, regardless of treatment duration, and recorded data on adverse events. Event rates were compared for ephedra/ephedrine groups vs. placebo groups, and a meta-analysis was conducted on those adverse event symptoms for which RAND concluded that an appreciable number of events were noted in the controlled trials. In addition, RAND reviewed those adverse event reports compiled by FDA that were filed prior to September 30, 2001 and that recorded reports of death, heart attack, stroke, seizure or serious psychiatric illness, as well as call records from Metabolife. RAND classified some of these reports as either "sentinel events" (as defined in the RAND Report), "possible sentinel events" or psychiatric cases.

A. Efficacy for Weight loss

RAND confirmed that for weight loss purposes, ephedra provides a significant increase in weight loss over the short-term (generally under six months).[19] The study provides that weight loss over the longer-term has not yet been researched and therefore has not yet been documented in clinical trials. As explained herein, however, longer-term research has, in fact, been conducted (See Section I.B., supra).

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[19] RAND's basis for defining "short-term" as generally under six months is not clear, particularly in light of FDA's own advisory committee recommending a study of 12 weeks duration to evaluate OTC weight loss drug products.

Specifically, RAND concluded that short-term use of ephedrine, ephedrine plus caffeine, or dietary supplements containing ephedra with or without caffeine is associated with a statistically significant increase in short-term weight loss (compared to placebo).[20] Moreover, the addition of caffeine to ephedrine is associated with a statistically significant modest increase in short-term weight loss over that attributable to ephedrine alone.[21] The study points out, "No studies have assessed the long-term effects of ephedrine or ephedra-containing dietary supplements on weight loss; the longest published treatment duration was six months."[22]

B. Safety

Significantly, RAND does not conclude that ephedra causes serious adverse health consequences. While the report found sufficient evidence from controlled trials to associate use of ephedrine and/or ephedra-containing herbal supplements or ephedrine plus caffeine with an increased risk of "mild to moderate" side effects including palpitations and gastrointestinal, psychiatric, and autonomic symptoms,[23] we note that these types of side effects have long been observed in ephedrine-containing and other OTC products regulated by the FDA. *See* Section V.B.7, infra.

Importantly, RAND did not reach a similar conclusion regarding serious adverse events.[24] On the contrary, RAND acknowledges the undisputed fact that "[n]o serious adverse events (e.g. death, myocardial infarction, stroke, etc.) were reported in the 52 clinical trials that reported sample sizes. Therefore, the rate for these adverse events is zero."[25] In addition, the report provides, "There were no reports of serious adverse events in the controlled trials of ephedrine or ephedra, but these studies are insufficient to assess adverse events that occurred at a rate of less than 1.0 per 1000." [26]

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[20] RAND Report, pp. 83-85, 219-20.

[21] RAND Report, p. 84.

[22] RAND Report, pp. vi., 219.

[23] White Paper.

[24] RAND Report, p. 221.

[25] RAND Report, p. 88.

[26] RAND Report, p. 221.

Moreover, RAND concludes that an assessment of case reports is insufficient to reach conclusions regarding causality. The report provides, "The most important limitation is that the study design (that is, an assessment of case reports) is insufficient for us to reach conclusions regarding causality."[27] Similarly, it summarizes its findings as follows: "Continued analysis of case reports cannot substitute for a properly designed study to assess causality."[28] Given the insufficiency of the existing case reports as a means of assessing causality, RAND concludes that in order to eliminate the possibility that rare events could be causally related, "[s]cientific studies (not additional case reports) are necessary in order to assess the possible association between consumption of ephedra-containing dietary supplements and these serious adverse events. Given the rarity of such events, a properly designed case control study would be the appropriate next step. Such a study would need to control for caffeine consumption."[29]

RAND's findings on safety are entirely consistent with those of the FDA. The agency has acknowledged that the agency does "not have definitive evidence that ephedra has caused serious injuries and deaths."[30]

C. Consumer Data

In order to place an assessment of anecdotal case reports into context, it is essential for FDA to estimate the number of individuals who ingest dietary supplements that contain ephedrine alkaloids each year. This critical piece of information is known, in scientific terms, as the "denominator" for case report analysis.

It is generally acknowledged that no definitive evidence is available to determine an exact denominator with any statistical validity. However, RAND noted that 2.5 million Americans may have used weight loss products containing ephedrine from 1996-1998.[31] RAND acknowledged that this estimate could be low.[32] Another indication that this estimate may be low is the fact that Metabolife alone has indicated that, since mid-1995, it has sold billions of tablets/caplets of its

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[27] RAND Report, p. 217.

[28] RAND Report Summary, pp. 6-7.

[29] RAND Report, p. 221.

[30] White Paper.

[31] RAND Report, p. 6.

[32] RAND Report, p. 6.

ephedra weight-loss products. RAND also noted that 2.8 million Americans may have used ephedrine-containing products to improve athletic performance over the past three years.[33] Based upon the above, it appears clear that millions of Americans use dietary supplements that contain ephedrine alkaloids each year. It is critical that FDA consider this important fact when assessing anecdotal case reports, and in evaluating whether such reports actually amount to nothing more than "background noise" reflecting events that occur in the general population.

III. The Four New "Studies" Cited by FDA, and Not Reviewed by RAND, are Subject to Significant Scientific Limitations

In its recently issued proposed rule, FDA indicated that more "scientific evidence" has been released subsequent to RAND's analysis. The "scientific evidence" cited by the agency, however, is merely an assortment of inconclusive analyses. None of these four analyses is a double-blind, placebo-controlled clinical trial of the type required to scientifically assess causation.

The first study, published in the *Annals of Internal Medicine*, was based on calls made to the American Association of Poison Control Centers ("AAPCC"). Such calls, however, are anecdotal and generally may not be used for causation analysis.[34] Moreover, the authors assumed ephedra sales account for only 0.82% of herbal product sales in the United States – a figure dismissed by the Council for Responsible Nutrition ("CRN") as "nonsense." In fact, in a press release CRN indicated that "[m]ore comprehensive data obtained from Nutrition Business Journal indicates that the true ephedra sales volume in 2001 was approximately 35% of total sales of herbal products."[35] In the second study, published in *Neurology*, the authors acknowledged that "the most obvious limitation of this study was statistical power," and the study only indicates that ephedra "may" be associated with stroke at doses higher than 32 mg/day.

The authors of the third study, published in *Mayo Clinic Proceedings*, acknowledged that the study "has the limitation of being an observational study and as such does not definitively establish the relationship between ma huang use and the risk of adverse cardiovascular events." Finally, the authors of the fourth study, published in *Clinical Pharmacology and Therapeutics,* only evaluated eight

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[33] RAND Report, p. 7.

[34] It is generally recognized that anecdotal data may only be appropriately used in causation analysis when the underlying events are not common in the general population. **See Section V.B.6.c.

[35] CRN Press Release, "CRN Praises FDA Analysis on Ephedra; Criticizes Article Used in Analysis" (March 7, 2003). (*See* Attachment 19). Note that we are not aware of the precise statistical method used by the Nutrition Business Journal to estimate ephedra sales in 2001.

healthy adults - - and the study was not even blinded or placebo-controlled. The authors acknowledged that "a limitation in interpreting these results is that the relative cardiovascular effects of the individual stimulants cannot be distinguished" and the "interpretation of the subjective results must be qualified by the lack of a placebo-control group in this study."

Even when combined, these four analyses provide no conclusive scientific evidence and at best are hypothesis-generating analyses.

A. The AAPCC Anecdotal Data Relied Upon in the "Annals of Internal Medicine" Study Are Incapable of Demonstrating Causation: Bent, S. T., *et al., The relative safety of ephedra compared with other herbal products,* 138(6) Annals of Internal Medicine 468 (Mar. 2003).

It is well-established that reports collected by passive surveillance systems, such as the systems operated by the AAPCC and FDA, cannot prove causation when the reported events are common in the general population. FDA's website, for example, posted a disclaimer that cautioned that "there is no certainty that a reported adverse event can be attributed to a particular product."[36] Further, Dr. Christine Lewis, the Director of FDA's Office of Nutritional Products, Labeling, and Dietary Supplements stated that AERs "do not offer proof that any supplement caused the death or illness listed, only that the person ingested the supplement before his or her death or injury."[37]

This study was based on passive collection of anecdotal data obtained through phone calls made to participating Poison Control Centers. A single observer, using unspecified criteria, determined the presence or absence of ephedra toxicity for a particular report. It is our understanding that the primary focus of this system is on helping the caller obtain medical information and assistance, not on tracking the details of the incident. It is also our understanding that it is generally not possible, based upon AAPCC data, to verify whether reported events were caused by a particular product.

The report published in the *Annals of Internal Medicine* reviewed adverse events allegedly associated with ephedra to calculate relative risk (the report reviewed the AAPCC Toxic Event Surveillance System Database Annual Report in 2001). In order to make this relative risk assessment, the

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[36] *The Special Nutritionals Adverse Event Monitoring System,* FDA CFSAN, Office of Special Nutritionals, *available at* http://vm.cfsan.fda.gov/~dms/aems.html.

[37] Tracy Wheeler & Jim Quinn, *Herbal Products Cause Ill Effects: Natural Remedies Can Prove Deadly*, Akron Beacon Journal, May 9, 2000 (citing Christine Lewis).

authors required an accurate estimation of the units of ephedra sold. Ignoring substantial marketing data, the authors assumed for purposes of their analysis that herbs such as valerian and kava have a higher percentage of sales than ephedra products. In fact, the authors assumed that ephedra-containing supplements account for less than 1% of the market for herbal supplements. Based upon all available data, this assumption is not even close to being accurate. In fact, as noted, in a press release CRN indicated that "[m]ore comprehensive data obtained from Nutrition Business Journal indicates that the true ephedra sales volume in 2001 was approximately 35% of total sales of herbal products." Based upon the dramatic undercounting of ephedra sales, the authors dramatically overstated the alleged relative risk of ephedra.

Finally, even regardless of the overstatement of potential risk, the report fails to prove that ephedra causes any health problems as the underlying data set is simply not scientifically appropriate for use in causation analysis.

B. The Authors of the Review Evaluating the Risk of Ephedra and Hemorrhagic Stroke Acknowledge that the Review Is Not Statistically Sufficient to Draw Any Conclusions Regarding Ephedra: Morgenstern, L. B., *et al.*, *Use of ephedra-containing products and risk for hemorrhagic stroke*, 60 Journal of Neurology 132 (2003).

The authors analyzed data from a study previously performed to examine the relationship between phenylpropanolamine (PPA) and hemorrhagic stroke. Based upon study results, the authors confirmed that ephedra is not associated with increased risk of hemorrhagic stroke, except possibly at doses of more than 32 mg per day. No new data was collected, and the original study was not intended to evaluate the safety of ephedra. There were only 7 cases, and 12 controls, that reported use of ephedra (and only 6 cases and 4 controls among the subjects who ingested more than 32 mg of ephedrine alkaloids per day).

Based upon the authors' own statements, it is clear that the above study was not intended, and cannot be used, to draw firm conclusions regarding the alleged potential risk of ephedra and hemorrhagic stroke. Rather, as acknowledged by the authors, the study is a preliminary "hypothesis-generating" study that requires further research to determine if there is an actual causative link.

Specifically, the authors acknowledged that the study did not have sufficient statistical power to draw any firm conclusions regarding an association between ephedra and hemorrhagic stroke. Due to the fact that the study was not designed to specifically examine ephedra, the study did not have an appropriate size or protocol to ensure statistically valid results. As a result, the study is merely able to theorize that there is an increased risk of hemorrhagic stroke among ephedra users

– it fails to demonstrate a statistically significant association between ephedra and stroke at any dosage levels.

C. The Authors of This Study Acknowledge That the Study is an Observational Study and Does Not Definitively Establish Causation: Samenuk D, *et al.*, *Adverse Cardiovascular Events Temporally Associated with Ma Huang, an Herbal Source of Ephedrine*, 77(1) Mayo Clinic Proceedings 12 (2002).

The authors of this study acknowledged that the study "has the limitation of being an observational study and as such does not definitively establish the relationship between ma huang use and the risk of adverse cardiovascular events." The study reviewed adverse event reports submitted to the FDA from January 1995 to January 1997 that were alleged to be related to supplements containing ephedra. As the study is based upon a review of FDA's anecdotal AERs, the conclusions are subject to the same scientific limitations that the Agency is well aware of with regard to anecdotal data and causation assessments.

Specifically, for each FDA AER, there is in practice little to no way of determining whether a specific substance caused the event in question, when the event is common in the general population. Moreover, even when viewed in the aggregate, there is an underlying baseline risk of disease that must be reflected in the analysis. As millions of Americans consume products that contain ephedrine alkaloids, a degree of background events coincidental with such use must be expected.

As noted, GAO reviewed the same FDA AERs in its 1999 report on ephedra products, and determined that they were not sufficient to prove a causal relationship between ephedra-containing products and serious cardiovascular events.

D. Results For This Study are Not Statistically Valid for Causation-Related Assessments: Haller, C.A., *et al.*, *Pharmacology of Ephedra Alkaloids and Caffeine After Single-Dose Dietary Supplement Use*, 71(6)Clinical Pharmacology and Therapeutics 421 (June 2002).

This study only entailed a review of eight adults, five women, and three men. Heart rate, blood pressure, renal clearance, and mood were evaluated based upon ingestion of a single dose of 20 mg ephedrine alkaloids and 200 mg caffeine. The study was not blinded or placebo controlled, and the subjects were informed in advance that they would be ingesting ephedra – resulting in potential bias with regard to the mood-related questions.

Based upon the small number of subjects, and the absence of blinding or placebo controls, this study can only be viewed as a preliminary "hypothesis generating" study. Study results are not statistically valid for causation-related assessments associated with ephedra.[38]

IV. "Unreasonable Risk" Standard: Statutory Requirements, Judicial Pronouncements, and Scientific Support

A. Statutory Standard under DSHEA

The Agency is obligated to follow the Congressional directives established in DSHEA. DSHEA was enacted to ensure that consumers "should be empowered to make choices about preventive health care programs based on data from scientific studies of health benefits related to particular dietary supplements."[39]

Congress carefully crafted DSHEA to ensure that the "unreasonable risk" standard does not operate in a vacuum. Specifically, according to DSHEA, FDA must determine whether a dietary supplement presents a "significant or unreasonable risk of illness or injury under conditions of use recommended or suggested in labeling."[40]

In other words, with regard to ephedra, FDA must apply this provision by evaluating specific indications for use and warning language contained on product labeling. Safety assessments are not conducted in the abstract, and FDA must evaluate product labeling and apply the "unreasonable risk" standard under the logical assumption that American consumers can understand and follow product labeling instructions and warnings. Any product can be abused or misused, and it would be inappropriate and contrary to the Congressional mandate under DSHEA for the agency to classify a product as an "unreasonable risk" based upon inappropriate product usage.

DSHEA also contains a carefully crafted construct with administrative and procedural safeguards. Specifically, DSHEA provides that "[i]n any proceeding under this subparagraph, the United States shall bear the burden of proof on each element to show that a dietary supplement is

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[38] We note that the authors indicate, in introducing the study, that other studies have reported that the pharmacokinetics of synthetic ephedrine and ephedrine in the form of ephedra extracts are similar.

[39] DSHEA Congressional Finding, DSHEA § 2(8) (emphasis added).

[40] DSHEA, § 4 (emphasis added).

adulterated." Moreover, DSHEA also provides that "[t]he court shall decide any issue under this paragraph on a de novo basis." Under the de novo review standard, a reviewing court need not give deference to, and may actually disregard, FDA's findings or conclusions. Moreover, FDA would have the burden of demonstrating that a product poses an unreasonable risk.

The term "unreasonable risk" implies that FDA should perform some calculus of the associated risks and benefits of a dietary supplement before it intervenes. Such an assessment, however, must be based upon prospective studies with appropriate controls, not anecdotal information. Accordingly, a review of the administrative record compels the conclusion that the benefits of using ephedrine alkaloids to support one's diet and weight loss program significantly outweigh any hypothetical serious risks. A product with proven benefits, and only hypothetical serious risks, may not pose an "unreasonable risk" under the DSHEA standard.

B. FDA Obligation to Ensure that its Regulatory and Scientific Safety Assessments are "Science Based"

1. General FDA Obligation to Ensure Regulations are Science-Based

It is axiomatic that all significant FDA regulatory decisions must be "science-based." FDA itself has clearly indicated that its product assessments must be based upon science and not political or media pressures. For example, FDA recently issued guidelines on information quality to the Office of Management and Budget entitled "Guidelines for Ensuring the Quality of Information Disseminated to the Public."[41] In these guidelines, the agency indicated that it is committed to taking steps to ensure that its "regulatory decisions are based on objective information." For "influential" scientific information such as the agency's analysis of ephedra, FDA has indicated that its review will be transparent with exposure of any potential biases.

Most importantly, FDA indicated that it will follow the general principles for risk assessments applied by Congress under the Safe Drinking Water Act Amendments of 1996, whereby the agency will adhere to use of: "the best available science and supporting studies conducted in accordance with sound and objective scientific practices, including peer reviewed science and supporting studies when available" and "data collected by accepted methods (if reliability of the method and the nature of the decision justify use of the data."[42]

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[41] *Guidelines for Ensuring the Quality of Information Disseminated to the Public, Part I, available at* http://www.hhs.gov/infoquality/fda.html#1 (hereinafter, "Information Quality Guidelines, Pt. 1").

[42] Information Quality Guidelines, Pt. 1.

Similarly, the Center for Food Safety and Applied Nutrition ("CFSAN"), in March, 2002, issued a report entitled "Initiation and Conduct of All 'Major' Risk Assessments within a Risk Analysis Framework: A Report by the CFSAN Risk Analysis Working Group." In this report, FDA indicated that risk assessments must be based upon sound science and not political pressure:

> Based on sound science. The risk assessment should be based on sound science that is decision driven and supported by systematic analysis that maintain integrity and protects the risk assessment from political and other pressure.[43]

The same report indicates that a "science advisor" must be utilized to ensure that the risk assessment "is not compromised by the policy needs of the risk management team."[44]

The report also indicates that FDA risk assessors must "ensure that the assessment is of high scientific quality and consistent with existing scientific practices for the conduct of risk assessments."[45] In fact, the report indicates that the development of data quality criteria must be consistent with the above-mentioned OMB-related scientific guidelines. The report notes that "'good' data are complete, relevant and valid; complete data are objective, relevant data are case-specific, and validation is time-dependent."[46]

In conclusion, FDA's risk assessment regarding ephedra must be based upon sound science and not hypothetical risks or conjecture. In addition, as discussed in Section IV.B., above, and in Section VI, below, product abuse and/or misuse are not legally appropriate factors for FDA to consider in evaluating whether a dietary supplement poses an "unreasonable risk" under the DSHEA standard.

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[43] *Initiation and Conduct of All "Major" Risk Assessments within a Risk Analysis Framework: A Report by the CFSAN Risk Analysis Working Group* (March 2002), *available at* www.CFSAN.fda.gov/~dms/rafw-1 html.

[44] *Id.*

[45] *Id.*

[46] *Guidelines for Ensuring the Quality of Information Disseminated to the Public, Part III, available at* http://www.cfsan.fda.gov/~dms/rafw-3.html (hereinafter, "Information Quality Guidelines, Pt. 3").

2. FDA Regulations Regarding Well-Controlled Clinical Trials and Anecdotal Data

Across the food, drug, and dietary supplement contexts, FDA has been consistent in stating that well-controlled, clinical studies are needed to determine whether a product is safe and/or effective, and that anecdotal data are insufficient for the same purpose. The FTC has reached a similar conclusion with regard to substantiation for dietary supplement advertising that, while not binding upon FDA, lends additional support to the agency's preference for such studies.[47] While the context for such determinations has typically involved efforts to prove that a substance is safe and/or effective, logic dictates that the same standard be applied to prove that a substance is not safe and/or effective. In light of continued reliance upon well-controlled, clinical studies to support decision-making in other contexts, it is clear that this standard must be similarly applied in any evaluation of the safety and effectiveness of ephedra.

FDA regulations, in many contexts, provide further instruction on the appropriate scientific process for evaluating whether there is an adequate scientific basis for evaluating ephedra's safety and efficacy.

a. Nutrition Labeling and Education Act ("NLEA") "Health Claims"

In the food context, FDA will promulgate regulations authorizing an NLEA health claim regarding the relationship between a food substance and a disease or health related condition only "when it determines, based on the totality of publicly available scientific evidence (including evidence from well-designed studies conducted in a manner which is consistent with generally recognized scientific procedures and principles), that there is significant scientific agreement,

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[47] While not binding upon the FDA, the Federal Trade Commission's *Dietary Supplements: An Advertising Guide for Industry* (hereinafter "FTC Guidelines") are also illustrative of the high scientific standard agencies require to evaluate the purported efficacy of a food substance. Under FTC law, before disseminating an advertisement, "advertisers must have a reasonable basis for all express and implied product claims." In most situations, "the quality of studies will be more important than the quantity." While the FTC will consider all forms of "competent and reliable" evidence, well-controlled human clinical studies are the most reliable form of evidence. Finally, the FTC has indicated that "[a]necdotal data about the individual experience of consumers is not sufficient to substantiate claims about the effects of a supplement. Even if those experiences are genuine, they may be attributable to a placebo effect or other factors unrelated to the supplement. Individual experiences are not a substitute for scientific research." FTC Guidelines, page 10 (emphasis added).

among experts qualified by scientific training and experience to evaluate such claims, that the claim is supported by such evidence."[48]

Elaboration on this standard is provided in FDA's *Guidance for Industry: Significant Scientific Agreement in the Review of Health Claims for Conventional Foods and Dietary Supplements* (hereinafter, "FDA Guidance").[49] "The standard of scientific validity for a health claim includes two components: 1) that the totality of the publicly available evidence supports the substance/disease relationship that is the subject of the claim, and 2) that there is significant scientific agreement among qualified experts that the relationship is valid."[50]

The significant scientific agreement standard is intended to be a strong one that "provides a high level of confidence in the validity of a substance/disease relationship."[51]

FDA has looked to two types of studies, interventional studies and observational studies, in evaluating the scientific evidence supporting food health claims.[52] The "gold standard" for interventional studies is the randomized well-controlled clinical trial. FDA Guidance. Observational studies, including case reports, are less preferable than interventional studies, in part because of their "limited ability to ascertain the actual food or nutrient intake for the population studied."[53] Observational data are also generally restricted to identifying associations between food substances and health outcomes, and often do not provide a sufficient basis for determining whether a substance/disease association reflects a causal rather than a coincidental relationship."[54]

To the extent that the FDA does look to observational studies as evidence of significant scientific agreement regarding a food-health relationship, it makes clear that these studies carry varying degrees of persuasiveness, and that case reports are the <u>least</u> persuasive type of observational

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[48] 21 C.F.R. 101.14(c); 21 U.S.C. § 343(r)(3)(B)(i).

[49] 64 Fed. Reg. 71,794 (1999).

[50] FDA Guidance.

[51] *Id.*

[52] *Id.*

[53] *Id.*

[54] *Id.* (Emphasis added.)

study.[55] Observational studies which are preferable to case reports, in descending order of persuasiveness, include: 1) cohort (longitudinal) studies, 2) case-control studies, 3) cross-sectional studies, 4) uncontrolled case series or cohort studies, 5) time-series studies, 6) ecological or cross-population studies and 7) descriptive epidemiology.[56]

Assessing scientific agreement relies on judging the extent of agreement among qualified experts. Such agreement occurs "well after the stage of emerging science, where data and information permit an inference" and "derives from the conclusion that there is a sufficient body of sound, relevant scientific evidence that shows consistency across different studies and among different researchers and permits the key determination of whether a change in the dietary intake of the substance will result in a change in a disease endpoint."[57]

The "significant scientific agreement" standard is met when "the validity of the relationship is not likely to be reversed by new and evolving science, although the exact nature of the relationship may need to be refined over time."[58] While such agreement does not require unanimous consensus, it represents considerably more than an initial body of emerging evidence. Such agreement cannot be reached without a "strong, relevant and consistent body of evidence on which experts in the field may base a conclusion that a substance/disease relationship exists. There is considerable potential for incorrect conclusions if only preliminary evidence (emerging science) is available for review."[59]

b. New Drug Application ("NDA") Requirements

FDA adheres to a similar scientific standard in assessing applications for new drug approvals. The FDA will refuse to approve a new drug application if there is insufficient information about the drug to determine whether the product is safe for use under the conditions prescribed, recommended or suggested in its proposed labeling, or there is a lack of substantial evidence

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[55] *Id.*

[56] *Id.*

[57] *Id.*

[58] *Id.*

[59] *Id.*

consisting of adequate and well-controlled investigations that the drug product will have the effect it purports or is represented to have.[60]

An adequate and well-controlled study has the following characteristics:

(1) A clear statement of the objectives of the investigation and a summary of the proposed or actual methods of analysis;

(2) A design that permits a valid comparison with a control, and a protocol for the study and report of results that describe the study precisely, accounting for such variables as duration of treatment periods, sample size, etc.;

(3) A method of selection of subjects that provides adequate assurance that they have the disease or condition being studied, or evidence of susceptibility and exposure to the condition against which prophylaxis is directed;

(4) A method of assigning patients to treatment and control groups that minimizes bias and is intended to assure comparability of groups with respect to pertinent variable such as age and sex;

(5) Measures taken to minimize bias on the part of subjects, observers and analysts;

(6) Methods of assessment of subjects' responses that are well-defined and reliable;

(7) Analysis of the results of the study adequate to assess the effects of the drug.[61]

Nowhere does the definition of an adequate and well-controlled study make reference to the inclusion of case reports as an acceptable methodology. Moreover, the regulations continue:

> Uncontrolled studies or partially controlled studies are not acceptable as the sole basis for the approval of claims of effectiveness. Such studies carefully conducted and documented, may provide corroborative support of well-controlled studies regarding efficacy and may yield valuable data regarding safety of the test drug. Such studies will be considered on their merits in the light of the principles listed here, with the exception of the

[60] 21 C.F.R. §§ 314.125(a)(4), (a)(5).

[61] 21 C.F.R. §§ 314.126 (b)(1)-(b)(7).

> requirement for the comparison of the treated subjects with controls. Isolated case reports, random experience, and reports lacking the details which permit scientific evaluation will not be considered.[62]

In the instant case, FDA does not point to a single adequate, well-controlled clinical study, to claim that ephedra-containing products are not safe or effective. In fact, we understand FDA cannot point to such a study, as RAND was not able to identify a single well-controlled clinical study, out of the more than 50 it reviewed, indicating a single serious event resulting from use of an ephedra-containing product.

C. Judicial Interpretation of the "Unreasonable Risk" Standard

DSHEA does not articulate any standard for assessing "unreasonable risk." However, in announcing its request for ephedra-related comments, FDA acknowledged the "legal standard of 'significant or unreasonable risk' implies a risk-benefit calculation based on the best available scientific evidence. It strongly suggests that the agency must determine if a product's known or supposed risks outweigh any known or suspected benefits, based on the available scientific evidence, in light of the claims the product makes and in light of the product's being sold directly to consumers without medical supervision."[63]

In the absence of an explicit substantive scientific standard for evaluating "unreasonable risk," FDA must be guided by precedent from other agencies. The term "unreasonable risk" has been used on many occasions, including in many cases involving the Consumer Product Safety Commission (interpreting the Consumer Product Safety Act, 15 U.S.C. § 2051 et seq.). A review of this case-law indicates that an assessment of an "unreasonable risk" must include:

- A required balancing of risks and benefits;
- A stringent burden on the agency to demonstrate that the product at issue poses an unreasonable risk of injury;
- More than reliance on mere consumer complaints and anecdotal data;
- Valid scientific data, sufficient to predict how likely an injury is to occur.

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[62] 21 C.F.R. § 314.126(e).

[63] FDA Press Release, February 28, 2003 (hereinafter, "FDA Proposed Rule Press Release"). (emphasis added).

Administrative agencies do not interpret statutory provisions in a vacuum. In the instant case, there is a long-established body of case-law interpreting the "unreasonable risk" standard, and such established case-law precedent may not be ignored. Accordingly, when interpreting the "unreasonable risk" provision under DSHEA, FDA must be guided by prior judicial decisions and acknowledge the high scientific threshold the Agency must overcome in order classify a product as an "unreasonable risk."

1. The CPSC "Unreasonable Risk" Standard

Whenever the Consumer Product Safety Commission (CPSC) finds that "a consumer product is being, or will be, distributed in commerce and such consumer product presents an unreasonable risk of injury" and "no feasible consumer product safety standard under this chapter would adequately protect the public from the unreasonable risk of injury associated with the product" the Commission may promulgate a rule declaring the product a "banned hazardous product."[64] Federal regulations illuminate the concept of "unreasonable risk" in the consumer product safety context:

> In determining whether a product presents an unreasonable risk, the firm should examine the utility of the product, or the utility of the aspect of the product that causes the risk, the level of exposure of consumers to risk, the nature and severity of the hazard presented, and the likelihood of resulting serious injury or death. In its analysis, the firm should also evaluate the state of the manufacturing or scientific art, the availability of alternative designs or products, and the feasibility of eliminating the risk.[65]

Here, the ultimate question in assessing unreasonable risk is whether the record contains "such relevant evidence as a reasonable mind might accept as adequate to support a conclusion."[66] The burden of demonstrating such evidence falls on the Commission, and the burden is a strict one.[67] Each requirement of the rule must be reasonably necessary to prevent or reduce an unreasonable

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[64] 15 U.S.C. § 2057.

[65] 16 C.F.R. § 1115.6(b).

[66] *Gulf South Insulation v. CPSC,* 701 F.2d 1137, 1143 (5th Cir. 1983) (citing *Aqua Slide 'N' Dive v. CPSC,* 569 F.2d 831, 838 (5th Cir. 1978)).

[67] *Id.*

risk of injury; if any part of the standard is not reasonably necessary, the whole standard must fail "unless the offending parts are set aside."[68]

Moreover, not only must the court look to the substance of the evidence in the administrative record in assessing whether substantial evidence exists to support the agency's rule; additionally, "the inability of any court to weigh diverse technical data also demands an inquiry to determine whether the Commission 'carried out [its] essentially legislative task in a manner reasonable under the state of the record before [it].'"[69] That is, the court must examine the agency's procedure in reaching its finding, as well as the substantive evidence in the record.

The CPSC is required by statute, prior to its issuance of any safety standard, to find not only "that the rule is reasonably necessary to eliminate or reduce an unreasonable risk of injury associated with [the] product," but also "that the promulgation of the rule is in the public interest," "that the rule imposes the least burdensome requirement which prevents or adequately reduces the risk of injury for which the rule is being promulgated," and "that the benefits expected from the rule bear a reasonable relationship to its costs."[70] The CPSA requires not only that the risk of injury be unreasonable, but also that the standard issued be "reasonably necessary to eliminate or reduce" the risk.[71] The necessity of the safety standard is dependent upon the nature of the risk, and the reasonableness of the risk depends on the burden a standard would impose on the user of the product; thus, the inquiry requires consideration of the costs to consumers, including increases in price, decreased availability of a product, and reductions in product usefulness. [72]

The CPSC must satisfy a stringent burden in order to establish that a risk is unreasonable and that its safety standard is reasonably necessary. Even where the Commission is able to identify a

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[68] *Aqua Slide*, 569 F.2d at 838 (holding that where CPSC issued a standard requiring warning signs, a ladder chain, and specific installation specifications for swimming pool slides, the warning sign provision should be set aside given that substantial evidence of its necessity had not been demonstrated).

[69] *Aqua Slide*, 569 F.2d at 838 (citation omitted).

[70] 15 U.S.C. §§ 2058(f)(3)(A), (B), (E), (F).

[71] *Aqua Slide*, 569 F.2d at 838; 15 U.S.C. § 2058(f)(3)(A).

[72] *Id.* at 839 (citing H.R. REP. No. 1153, at 33 (1972)).

potential problem through consumer complaints, such evidence, alone, is not sufficiently substantial to support a finding of unreasonable risk of injury.[73]

In *Gulf South*, the CPSC issued a final rule banning urea-formaldehyde foam insulation (UFFI) in residences and schools after a six-year investigation concluded, in the Commission's view, that UFFI presented an unreasonable risk of injury from irritation and cancer and that no feasible product standard existed that would adequately protect the public from those hazards.[74] In conducting its study, the agency obtained the results of in-home testing to determine the average levels of formaldehyde in UFFI homes and non-UFFI homes and also arranged testing on a number of commercially available UFFI products in simulated wall panels.[75] In order to investigate the link between exposure to formaldehyde and acute irritant symptoms, the Commission spent two years investigating and gathering information from 350 homes whose occupants had complained of adverse health effects related to UFFI, concluding that "taken as a whole, the complaints do identify a real problem."[76] In addition, the agency commissioned the National Academy of Sciences to conduct a literature review and determine whether there is a level of formaldehyde exposure below which no acute symptoms will be experienced.[77] The NAS' Committee on Toxicology concluded that there was no such threshold. *Id.* Finally, the agency extrapolated data from high exposure rat studies, using a computerized mathematical risk assessment model to quantify the risk of cancer to humans at the low levels of formaldehyde exposure associated with UFFI.[78] On the basis of all of the above-mentioned studies and analysis, the Commission concluded that UFFI poses an unreasonable risk of cancer to humans, which, coupled with its finding of an unreasonable risk of acute irritant effects, led the Commission to initiate a ban on UFFI.[79]

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[73] *Gulf South*, 701 F.2d at 1147-48 (holding that, where the Commission had failed to quantify the risk associated with the product, complaints regarding effects of urea-formaldehyde foam insulation (UFFI) were insufficient to support a finding that the product posed an unreasonable risk of injury from irritation and cancer, and could not support banning the product from residences and schools).

[74] *Id.* at 1139.

[75] *Id.* at 1140-41.

[76] *Id.* at 1141.

[77] *Id.*

[78] *Id.* at 1141-42.

[79] *Id.* at 1442.

Upon review, the court rejected the Commission's conclusion. Industry had heavily criticized the Commission's findings, asserting: 1) that the formaldehyde levels found in the test homes and lab tests were not accurate indicators of the levels in average UFFI homes, and 2) that the Commission erred in relying exclusively on rat data and ignored numerous epidemiologic studies indicating that formaldehyde is not a human carcinogen.[80] While the court found that the in-home and lab studies upon which CPSC relied did suggest that UFFI "appreciably raises in-home formaldehyde levels," the Commission had not used the studies "only to support such a generalized finding."[81] Rather:

> They were also incorporated into an exacting, precise, and extremely complicated risk assessment model. The goal of the model was to determine the risk of cancer to a consumer living in an average UFFI home. The difficulty in reaching this goal is that neither the in-home nor the [lab] studies were consistent with this aim. The in-home study focused on complaint residences, not average residences, not randomly selected residences. The [lab] studies reflected conditions similar to an unheated, unair-conditioned home, not an average home. The similar results achieved by the two studies validate neither. The studies were inadequate to serve as a data base for the [computerized model].[82]

The court also criticized the Commission's reliance on the 11 epidemiologic studies that were included in the record, involving a total of 10,000 workers.[83] While the court acknowledged that the studies advocated by industry did not demonstrate conclusively that formaldehyde was cancer-risk-free, the court also pointed out that the Commission, relying on its own studies, had concluded that the increased risk of cancer from exposure at the levels it attributed to UFFI was

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[80] *Id.* at 1443. Industry made additional assertions that the Court did not find necessary to examine in detail: 1) that the Commission ignored the real explanation for the incidence of tumors at the high levels of formaldehyde exposure in the rat study; 2) that no substantial evidence supported the Commission's assumption that the effective formaldehyde dose for humans is the same as that for rats; 3) that the computerized risk assessment program used incorporated assumptions about carcinogenicity that were not supported by substantial evidence, 4) that the model predicted only an upper limit of risk and did not constitute substantial evidence that "it is at least more likely than not that [UFFI] presents a significant risk of [cancer]"; and 4) that other federal agencies had determined that formaldehyde does not pose a substantial health risk to man. *Id.*

[81] *Id.* at 1145.

[82] *Id.* (emphasis added).

[83] *Id.*

up to approximately 1 in 20,000 (51 in a million).[84] The court concluded "it is highly unlikely that studies involving a total of 10,000 workers would detect such a small risk" and noted that the studies were less useful than they might otherwise have been because the did not consider the length or levels of exposure.[85]

Finally, the Court rejected the Commissions' reliance on consumer complaints, both as a basis for its computerized findings on cancer risk and as a measure of the risk of acute irritant effects. First, the court indicated that use of the complaints as a database for the computerized model was inadequate:

> The predictions made by the risk assessment model are no better than the data base. We have concluded that this base was inadequate. The Commission improperly relied on in-home data gathered largely from complaint homes. It failed to conduct a controlled study of randomly selected residences. The result is that the Commission's finding that UFFI poses an unreasonable risk of cancer is not supported by substantial evidence on the record as a whole.[86]

Second, the in-home investigations, from which the Commission concluded that inhabitants of UFFI homes suffered from a variety of acute effects including skin irritation, headaches and dizziness, did no more than identify a problem and could not justify a ban.[87] *Gulf South* makes clear that complaints must not merely demonstrate a risk of injury, but must answer the question whether the risk of injury is an unreasonable one.[88] This inquiry involves a balancing test, and a regulation may only issue if the "severity of the harm that may result from the product, factored by the likelihood of injury, offsets the harm the regulation imposes upon manufacturers and consumers."[89] Consumer complaints, alone, fail to tip the scales in favor of regulation, because

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[84] *Id.* at 1146.

[85] *Id.*

[86] *Id.* at 1147. (emphasis added).

[87] *Id.* at 1147-48.

[88] *Id.* at 1148.

[89] *Id.*, citing *Southland Mower v. CPSC*, 619 F.2d 499, 508-09 (5th Cir. 1980) (holding that a safety standard for walk-behind lawn mowers was reasonably necessary and in the public interest, while a requirement of a discharge chute foot-probe test was not supported by substantial record evidence as required).

they fail to demonstrate the critical second factor: the likelihood that injury will occur.[90] Failure to quantify the risk at the exposure levels actually associated with a product has been dubbed by at least one court as the "Achilles heel" in a finding of unreasonable risk: "Predicting how likely an injury is to occur, at least in general terms, is essential to a determination of whether the risk of that injury is unreasonable."[91]

As such, the agency's studies are critical in assessing whether there is substantial evidence that a product constitutes an unreasonable risk. Evidence as to the magnitude and likelihood of injury is of particular significance, and the courts will be critical of studies that it deems not to be reliable: "It must be remembered that the statutory term 'unreasonable risk' presupposes that a real, and not a speculative, risk be found to exist and that the Commission bear the burden of demonstrating the existence of such a risk before proceeding to regulate."[92] In *Southland Mower,* the CPSC sought to require a foot-probe test of lawn mowers to prevent what it deemed an unreasonable risk of blade-contact injuries.[93] CPSC relied, in part, on a study of 36 such injuries, one of which (three percent of the total) involved the specific type of accident CPSC sought to prevent.[94] The court rejected the study, noting:

> [T]he study did not involve a random sample, and it is not possible to extrapolate the percentage of total blade-contact injuries represented by discharge-chute incidents involving the operator's feet from the limited information furnished in the record. In any event, trustworthy statistical inferences cannot be drawn from a single incident of discharge-chute injury. Without reliable evidence of the likely number of injuries that would be addressed by application of the foot-probe test to the discharge chute, we are unable to agree that this provision is reasonably

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[90] *Id.*

[91] *Id.* at 1148. (emphasis added).

[92] *Southland Mower,* 619 F.2d at 510. (Emphasis added).

[93] *Id.* at 509-10.

[94] *Id.*

> necessary to reduce or prevent an unreasonable risk of injury. (emphasis added).[95]

It is clear that in both *Gulf South and Southland Mower*, the court clearly believed that a risk of injury existed – UFFI *did* cause an appreciable increase in in-home formaldehyde levels, and an unprotected lawn mower blade clearly had the potential to cause injury to feet coming into contact with it. The question for these courts was not whether a risk of injury existed, but what the magnitude and likelihood of such injury were; i.e. – was the risk an *unreasonable* one?

In the present case, however, there has not yet been any proof that ephedrine-containing products pose any serious risks at all. In fact, RAND reviewed 52 clinical trials, none of which identified a single serious adverse event; RAND therefore noted that the rate of such adverse events was zero. The question of "reasonableness" presupposes an existing risk, and in the absence of proof of the existence of a risk, such a question is moot.

2. The Standard Under DSHEA Is Even More Stringent Than The CPSC Standard

Unlike the "substantial evidence" test laid out by the CPSC, DSHEA explicitly mandates that FDA bear the burden of proof on each element to establish that a dietary supplement presents an unreasonable risk of illness or injury.[96] Moreover, it requires that the court review any FDA decision under the Act on a de novo basis.[97] This is a considerably higher standard than that imposed upon the CPSC; as such, the FDA faces an even more difficult burden in the instant case.

Importantly, the term "unreasonable risk" presupposes a real risk, not a hypothetical one. As noted in the above cases, in order for an agency to comply with the statutory burden to classify a risk as being "unreasonable," more than mere anecdotal reports must be identified. Courts have repeatedly held that agencies must rely upon scientific data in classifying a risk as "unreasonable." Moreover, courts have indicated that an agency must be in a position to quantify the degree of risk via scientific data. As one court noted: "Predicting how likely an injury is to occur, at least

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[95] *Id.* at 510, citing *D.D. Bean & Sons Co. v. CPSC*, 574 F.2d 643, 650-51 (1st Cir. 1978) (holding that absence of relevant injury data associated with particular hazards renders requirements of safety standard addressed to them invalid).

[96] 21 U.S.C. § 342(f).

[97] *Id.*

in general terms, is essential to a determination of whether the risk of that injury is unreasonable."[98]

As explained in more detail in Section V, below, in the instant case the science clearly supports the conclusion that ephedra produces weight loss. Moreover, as acknowledged by RAND, the scientific data are insufficient to conclude that ephedra poses any serious health risks. If a product has proven benefits, and only hypothetical serious risks – with no scientific data to demonstrate that any serious risks exist, let alone providing sufficient information to demonstrate the likelihood of such hypothetical risks – the judicial standard clearly warrants the conclusion that such a product does not pose an "unreasonable risk."

V. Science-Based "Unreasonable Risk" Standard Applied to Ephedra

A. Efficacy for Weight loss

1. The Problem of Over-weight and Obesity in the United States[99]

With regard to dietary supplements used to support weight loss objectives, it should be emphasized that the Surgeon General has indicated that over-weight and obesity have reached epidemic proportions. An estimated 61 percent of U.S. adults are over-weight or obese[100]. Moreover, over-weight and obesity constitute the second leading cause of preventable death, after smoking, resulting in an estimated 300,000 deaths per year at a cost (direct and indirect) that exceeds $100 billion a year.[101] Accordingly, the Surgeon General indicated that "[b]oth the

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[98] *Gulf South*, 701 F.2d at 1148.

[99] Statements regarding societal health problems associated with obesity in no way reflect the intended use of dietary supplements that contain ephedrine alkaloids (FDA prohibits dietary supplements from making claims to treat obesity, but permits weight loss claims). References to obesity are provided solely to reflect the general importance of losing and maintaining weight, and potential health concerns associated with being overweight but not necessarily obese.

[100] *The Surgeon General's call to action to prevent and decrease overweight and obesity*, U.S. Department of Health and Human Services, Public Health Service, Office of the Surgeon General (2001) (hereinafter, "Call to Action"), at p. XIII, *available at*, http://www.surgeongeneral.gov/topics/obesity/.

[101] Call to Action, at pp. XIII, 10. In addition, there have been a number of large-scale studies on morbidity and mortality issues in people of increased body mass index that indicate the dramatic impact of obesity on morbidity and mortality. *See, e.g., Body-Mass Index and Mortality in a Prospective Cohort of U.S. Adults*, 341 New Eng. J. Med. 1097 (Oct. 7, 1999).

prevention and treatment of over-weight and obesity and their associated health problems are important public health goals."[102]

More recently, the RAND Report contains an entire section devoted to the problem of obesity and being over-weight. RAND reports that "[f]rom 1999 through 2002, the prevalence of obesity increased by 1 percent per year, reaching a level of 19.8 percent among the adult population."[103] RAND also noted that according to one definition, "the majority of Americans (56 percent) were over-weight."[104]

With regard to health risks, the RAND Report provides the following:

> In addition to Type 2 diabetes, other serious health risks are associated with obesity. Rates and severity of hypertension, dyslipidemia, insulin resistance (Syndrome X), coronary artery disease, stroke, sleep apnea, osteoarthritis, certain cancers, and other conditions increase with increasing weight. Further, obesity increased the rate of mortality as well as morbidity, especially mortality associated with heart disease and diabetes. Using data from five large prospective cohorts, Allison and colleagues estimated that in 1991, 280,000 deaths were attributable to excess weight. Patients with a BMI greater than 30 accounted for more than 80 percent of obesity-attributable deaths.[105]

Finally, RAND emphasized that losing weight reduces the risk of negative health outcomes. RAND noted that "[i]ntentional weight loss by obese persons leads to reductions in risk factors for disease. A minimum loss of 5 percent to 10 percent of body weight followed by long-term weight maintenance can improve health outcomes."[106]

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[102] Call to Action, pp. V, XIII.

[103] RAND Report, p. 5.

[104] RAND Report, p. 5.

[105] RAND Report, p. 5. (Emphasis added).

[106] RAND Report, p. 6.

Based upon the above, the proven benefit of ephedra, with caffeine, to produce weight loss must be significantly reflected in any scientifically appropriate risk/benefit analysis. Losing weight results in significant health benefits.

2. Ephedra Produces Substantial Weight loss of up to Two Pounds per Month, for up to Six Months

In its recently issued report on ephedra, RAND indicated that it reviewed 59 articles that correspond to 52 controlled clinical trials of ephedrine or herbal ephedra for weight loss or athletic performance enhancement, and 46 of the studies were controlled trials assessing ephedra or ephedrine for weight loss.

After conducting this detailed review, RAND concluded that short-term use of ephedrine, ephedrine plus caffeine, or dietary supplements containing ephedra with or without caffeine is associated with a statistically significant increase in short-term weight loss compared to placebo. RAND also concluded that adding caffeine to ephedrine results in a statistically significant increase in the amount of weight loss.[107]

RAND concluded that the weight loss generated by such ephedra-containing supplements is approximately two pounds per month greater than with placebo – for up to four to six months.[108] This is a highly significant conclusion for the health of the American public.

On July 25, 2002, the Committee on Government Reform conducted a hearing on "Diet, Physical Activity, Dietary Supplements, Lifestyle and Health." During that hearing, George A. Bray, MD, one of the leading obesity and weight loss experts in the United States, testified that small weight loss, even over a short period of time, can be highly beneficial to health:

> Small weight losses can be highly beneficial in reducing the risk for the diseases I described earlier. In a study of which we are a part that is funded by the National Institutes of Health, called "The Diabetes Prevention Program," weight losses of 3 to 7 percent reduced by 58 percent and 31 percent the risk of people who are at high risk for diabetes from actually becoming diabetic. If you translate that into a 3-year delay in the complications of this

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[107] RAND Report Summary, p. 5. As the RAND report notes, in its introduction, caffeine alone has been shown to stimulate weight loss, both as an isolated alkaloid and as a botanical tea. RAND Report, p. 10.

[108] RAND Report, p. vi.

> disease, it saves billions of dollars by reducing the risk for human dialysis, for renal failure, for amputations, for blindness and other complications associated with diabetes. So modest weight losses can be highly beneficial. The dietary supplements that are available, particularly the ephedra-caffeine combinations have clear evidence from clinical trials of up to 6 months suggesting that the weight loss in the treating group is substantially larger than placebo and in the range that would be associated with these reductions in risk that were demonstrated in diabetes prevention programs.[109]

It can be informative to consider the extent to which RAND found that ephedra/caffeine products support weight loss in the context of FDA-approved prescription drugs intended to treat obesity.[110] Certain FDA-approved prescription drug products, for example, have been promoted as producing up to 10-14 pounds of weight loss per year. While in no way intended to suggest comparative efficacy, this provides some context to support the conclusion that the weight loss provided by dietary supplements containing ephedrine alkaloids (up to two pounds per month, for up to six months) is significant and should not be discounted.

3. Six Months of Weight loss is Highly Significant, and Exceeds the Recommendation of FDA's Own Advisory Committee for OTC Drugs

FDA and RAND repeatedly characterized the weight loss research conducted on ephedrine and caffeine as being "short-term" in nature and not sufficient to demonstrate weight loss benefits. For example, in its White Paper, FDA indicated that "none of these studies included treatment for more than 4 to 6 months or any follow-up after the product was stopped; there is therefore no evidence on the critical question whether there is a long-term weight loss effect that would translate into significant health outcome improvements."

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[109] *Diet, Physical Activity, Dietary Supplements, Lifestyle and Health: Hearing Before the House Committee on Government Reform,* 107th Cong 71 (2002) (testimony of George A. Bray, M.D.) (hereinafter, "Bray Testimony"), p. 71.

[110] References to prescription drugs intended to treat obesity are providing for background information and context only. Dietary supplements that contain ephedrine alkaloids are not intended to treat obesity, and as dictated by Congress are not subject to the prescription drug regulatory regime. Metabolife does not contend that Metabolife 356®, or any other dietary supplements, are in any way comparable to prescription drugs approved for marketing by the FDA.

The suggestion that a six-month weight loss study is not sufficient to demonstrate product efficacy is not consistent with prior FDA precedent regarding this issue. As the Agency is aware, the OTC Drug Review includes a weight loss monograph, which was intended to determine whether weight loss drug products are safe and effective for their intended use.

In the context of evaluating weight loss data, FDA's Advisory Review Panel on OTC Miscellaneous Internal Drug Products, developed a recommended study protocol for evaluating weight loss ingredients.[111] The scientifically valid protocol developed by FDA's own advisory review panel was 12 weeks in length – three months shorter than the research RAND confirmed establishes efficacy over a six-month period.[112]

In determining the appropriate duration of a weight loss clinical trial, the Advisory Review Panel assessed the applicable scientific concerns. The Federal Register notice provides:

> Design of the Study. The first problem facing the Panel in developing the design of the study was deciding upon the duration of it. Many of the studies reviewed in the drug companies' submissions lasted only 3 to 4 weeks. Even in the extensive review supplied by the FDA, only a few studies exceeded 6 weeks. The Panel was of the opinion that the study it was developing should be of sufficient duration so that, not only would weight reduction be established, but also the maintenance of it would be established. A drug is effective if it is instrumental in reducing weight and in aiding the individual to maintain the weight loss. It was decided that a study of 12 weeks duration would satisfy the Panel's goal.[113]

If 12 weeks was deemed to be sufficient to establish the efficacy of weight loss OTC drugs, there should be little doubt that 24 weeks (6 months) of scientific evidence for a dietary supplement to support weight loss in the over-weight population should be sufficient to establish product efficacy.

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[111] 47 Fed.Reg. 8466, 8480 (1982).

[112] *Id.*

[113] *Id.* at 8482 (emphasis added). The study design proposed by the Advisory Panel was a randomized placebo-controlled double-blind design incorporating the features of both a crossover and parallel sample design.

In addition to the above, it should be noted that many experts indicate that most weight loss is experienced in two to three month cycles. This type of "event" weight loss (for summer-time, weddings, reunions, after holidays, etc.) is common and provides significant health benefits. Experts indicate that even a five percent weight loss over the short-term can have a significant impact on health.[114] In fact, a recent study indicates that even attempted weight loss may be associated with lower mortality, independent of weight change[115]. Dietary supplements are not intended to treat obesity, and therefore short-term "event" weight loss and weight maintenance are some of the types of benefits dietary supplements should provide.

4. There is No Scientific Reason to Assume Weight loss Benefits will not Continue Beyond Six Months

As an initial matter, as indicated in Section I.B. herein, a number of studies have included subjects who have used ephedrine alkaloids over a six-month period. The results from these studies have been uniformly favorable. In addition, from a scientific perspective, there is no reason to believe the weight loss benefits associated with ephedrine alkaloids (with or without caffeine) would cease after a six-month time period. RAND indicated that it had not evaluated any studies longer then six months in duration, but never expressed the view that the absence of such data precludes the possibility that ephedrine would continue to work beyond the stated time period. Moreover, based upon the chemical activity of ephedrine alkaloids, we are unaware of any scientific reason for the ingredient to lose effectiveness after six months of product use.

Significantly, as noted above, studies have evaluated ephedrine alkaloids for time periods longer than six months. For example, a recent study was presented at the IX International Congress on Obesity in Sao Paolo, Brazil found that supplementation of ephedrine/caffeine (20 mg/day of ephedrine and 200 mg/day of caffeine) for 11 months after a 4-week dietary weight loss program allowed subjects to maintain weight loss while subjects taking a placebo regained the weight. Similarly, the study by Toubro, *et al.*, noted above, found that an ephedrine/caffeine compound (20 mg of ephedrine and 200 mg of caffeine) taken three times a day one hour before meals, improved and maintained total weight loss during 50 weeks, increasing fat loss and saving lean body mass, and caused only temporary minor side effects such as tremor and insomnia.[116] In addition, the study by Daly, *et al*, also noted above, reported that, for six subjects who remained on a combination of ephedrine (75-150 mg), caffeine (150mg) and aspirin (330) mg in divided

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[114] Bray Testimony, p. 74.

[115] *See* Gregg, (Attachment 18).

[116] *See* Toubro, (Attachment 15).

premeal doses, in an open-label trial for 7 to 26 months following the initial 8-week double blind placebo-controlled trial, the ECA combination was safe and generally well tolerated, and resulted in small but significant amounts of weight loss in five of the subjects, without calorie restriction.[117]

5. A Sufficient Number of Subjects Participated in the Studies to Demonstrate Weight loss Efficacy

Based upon our understanding of the RAND report, it appears as if RAND only considered 20 of the controlled clinical trials in assessing weight loss efficacy (out of 46 controlled studies that addressed this issue). Despite the reduction in the number of studies, based upon our reading of the RAND report, it is our understanding that the 20 clinical studies analyzed by RAND still included close to 1,000 subjects - of whom at least half consumed ephedrine alkaloids.

In this regard, it should be noted that even under the NDA process, FDA does not always require clinical trials to evaluate thousands of subjects. Rather, FDA uses its discretion to determine an appropriate number of subjects to establish drug efficacy or safety. FDA's "CDER Handbook" (available on the FDA website) has indicated that "Phase 3 studies usually include several hundred to several thousand people." For example, on September 26, 2000, FDA approved a "new drug" via the NDA process based upon clinical studies conducted on only 40 patients.[118]

In addition, under the OTC Drug Review, FDA has determined that numerous OTC drug ingredients are effective and/or safe in the absence of large clinical trials even approaching one thousand (or even a few hundred) subjects. In fact, FDA regulations do not provide a minimum number of subjects required to demonstrate product efficacy for all products under the OTC Drug Review.

Finally, FDA's own OTC drug weight loss advisory committee recommended a 12-week weight loss trial that would include 25 people in four separate study groups. Certainly, a review of data on what we believe to be near 1,000 subjects, from 20 consistent clinical trials, should be at least equally as persuasive as the data-set recommended by FDA's own advisory committee.

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[117] *See* Daly, (Attachment 14).

[118] Trisenox was approved as an orphan drug to treat leukemia.

B. Safety Profile of Ephedrine/Caffeine

1. RAND Analysis

In its recently issued report on ephedra, RAND indicated that it identified no serious adverse events in the 52 clinical trials regarding ephedrine it reviewed. In other words, the rate for such adverse events is zero. Moreover, RAND acknowledged that the strongest evidence for conducting causal assessments should be from clinical trials. In addition, FDA has indicated that OTC drugs that contain ephedrine alkaloids also have favorable risk-benefit ratios – even though such products provide a greater level of ephedrine alkaloids than ephedra-containing dietary supplements.

As part of its review, RAND spent a significant amount of time reviewing call records and FDA's adverse event reports in order to determine if a causal link can be demonstrated between serious adverse events and ingestion of dietary supplements that contain ephedrine alkaloids. RAND concluded that an assessment of anecdotal reports does not permit one to reach any conclusions regarding causality. RAND specifically noted that "[s]cientific studies (not additional case reports) are necessary in order to assess the possible association between consumption of ephedra-containing dietary supplements and these serious adverse events."[119]

RAND's conclusion therefore appears identical to the conclusion previously reached by the FDA regarding the use of anecdotal reports to determine causality. Specifically, in his June 14, 2002, letter to Sidney Wolfe, Secretary Thompson indicated that the "FDA advised [him] that the types of observed outcomes reported in relationship to the ingestion of ephedrine alkaloids are not uncommon in the general population and therefore the reports alone do not provide a scientific basis for assessing the safety of ephedrine alkaloids or establish a link between the reported events and the ingestion of ephedrine alkaloids." Since that letter was issued, RAND has reviewed additional anecdotal reports and has reached a similar conclusion.

2. NIH Working Group Analysis

On February 26, 2003, the National Institutes of Health, National Advisory Council for Complementary and Alternative Medicine (NACCAM) Working Group on Ephedra ("NIH Working Group") evaluated a draft version of the RAND Report, and concluded that the data on ephedra safety is inconclusive – it cannot be demonstrated, based upon current data and information, that ephedra is not safe. On March 17, 2003, the NIH Working Group suggested

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[119] RAND Report, p. 221

initiation of multi-site, prospective case-control study to assess the risk associated with taking ephedra. The NIH Working Group estimates that the proposed study would take 4-8 years, and cost $2-4 million per year.

3. Cantox Analysis

The purpose of the Cantox Report[120] was to critically review information related to the safety of ephedrine alkaloids. The information reviewed included the scientific literature on herbal ephedrine alkaloids and synthetic ephedrine (recognizing and taking into account the differences and similarities between the two), including clinical studies, toxicology studies, animal studies, published case reports, and FDA's AERs. Notably, Cantox also reviewed and took into consideration clinical studies concerning combination products, such as those containing herbal ephedrine alkaloids or synthetic ephedrine and caffeine. The focus of the assessment was on well-controlled human studies - as they provide the most reliable evidence.

Using this information, Cantox calculated a "no observed adverse effect level" of 90 mg/day and a "lowest observed adverse effect level" of 150 mg/day. The "no observed adverse effect level" is the level at which the studies reported no statistically significant increase in the frequency of adverse effects compared to placebo. The "lowest observed adverse effect level" is the level at which the studies showed a slight statistical difference, but no significant difference, in the frequency of adverse effects compared to placebo.

Importantly, the "lowest observed adverse effect level" of 150 mg/day, is 50% higher than the maximum daily dose of ephedrine alkaloids recommended by industry (100 mg/day), and even at that level, no life-threatening or debilitating effects were observed. The adverse effects observed at that level (*e.g.*, dry mouth, agitation, insomnia, headache, weakness, palpitation, tremor, giddiness, and constipation) were only moderate in intensity and did not persist throughout the studies. Notably, Cantox's observations regarding the mild nature of the side-effects of ephedrine at 150 mg/day are consistent with those of FDA in the preamble to the monograph for asthma products containing ephedrine.[121] Moreover, RAND reviewed the Cantox analysis as part of its own review and, like Cantox, determined that there is no scientific rationale to conclude that there is a causal link between ephedrine-containing products and serious adverse effects.

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

[121] *See* 51 Fed. Reg. at 35331 (setting a dosage limit of 150 mg/day of ephedrine).

Given that Cantox concluded that all of the relevant scientific data indicates that dietary supplements containing ephedrine alkaloids are safe at dosages of 90 mg/day and 150 mg/day, it is clear that the maximum daily dose recommended by industry of 100 mg/day is appropriate.

4. Demonstration of Safety under the OTC Drug Review

In the context of the OTC Drug Review, FDA concluded that ephedrine provided at daily levels that substantially exceed the levels provided in dietary supplements is "generally recognized as safe and effective" for its intended use. Moreover, FDA has indicated that such OTC drugs have not been associated with serious adverse events. FDA's February 28, 2003 press release provides:

> Ephedrine has long been available in some FDA approved over the counter and prescription drugs. It appears that the more controlled availability of synthetic ephedrine products, which are available primarily for approved uses for respiratory symptoms and carry mandatory warning labels, has not been associated with the same kind of severe adverse events as have occurred with dietary supplements containing ephedra.[122]

Based upon this longstanding OTC drug usage, the lack of severe adverse event reports linked to OTC ephedrine-containing drugs, and FDA's conclusion that ephedrine at such elevated levels is generally recognized as safe, it is difficult to comprehend how the agency could even begin to scientifically justify the allegation that ephedra poses an "unreasonable risk" at levels far lower than those already approved by the Agency.

Specifically, ephedrine-containing drugs are available at daily ephedrine dosage levels that exceed the level of ephedrine provided by dietary supplements that contain ephedrine alkaloids. For example, FDA-approved bronchodilators that contain ephedrine, under FDA's OTC Drug Review, can contain 12.5 to 25 mg ephedrine every four hours, not to exceed 150 mg in 24 hours.[123] Responsible members of the dietary supplement industry include up to 25 mg of ephedrine per serving, up to 100 mg in 24 hours. FDA specifically stated that, in studies, dosages of ephedrine at 25 mg every four hours (150 mg/day) had "little or no effect on the heart beat or blood pressure of adult asthmatics" and adults experienced only mild side-effects, including

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[122] FDA Proposed Rule Press Release.

[123] 21 C.F.R. § 341.76(d)(1).

"tenseness, nervousness, tremor, sleeplessness, loss of appetite, nausea, and difficulty in urination in older males who may have an enlarged prostate gland."[124]

Moreover, at least one expert has indicated that ephedrine from the ephedra plant may be absorbed into the bloodstream more slowly than the synthetic ephedrine found in these OTC drug products.[125] Thus, if anything, the likelihood that ephedrine would be present in the body at levels sufficient to cause adverse events can be expected to be higher in OTC drug products than in dietary supplements containing ephedrine from ephedra plant products. It is difficult, then, to comprehend how lower levels of ephedrine alkaloids could present a safety problem in dietary supplements while a higher level in OTC drugs do not.[126]

In addition, there is no duration of use limitation on OTC bronchodilator drugs that contain ephedrine. Unlike many OTC drug products, FDA has not seen fit to mandate a labeling statement along the lines of "do not take for more than 7 days" – and to our understanding the absence of such a duration of use has not led to reports of safety problems with OTC drugs that contain ephedrine. Moreover, it is our understanding that bronchial asthma is a condition amenable to long-term treatment and long-term preventative measures. It is difficult to comprehend how the absence of a duration of use for dietary supplements that contain ephedrine alkaloids could present a safety problem while OTC drugs for bronchial asthma also have no limitation on duration of use and have not presented problems (despite providing more ephedrine alkaloids on a daily basis than the dietary supplements).

It should also be noted that OTC drug products that contain ephedrine have not been contraindicated by the FDA for use with other products that contain caffeine. Although such OTC drugs do not *contain* caffeine, FDA has not seen fit to mandate warnings advising against

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[124] 51 Fed. Reg. 35326, 35531 (1986). *See also* 21 C.F.R. § 341.76(d)(1) (2001) (prescribing a dosage limit for ephedrine in bronchodilator drug products of 12.5 to 25 mg every 4 hours, not to exceed 150 milligrams in 24 hours); 21 C.F.R. §341.80(d)(1)(ii) (2001) (prescribing a dosage limit for pseudoephedrine (used as a nasal decongestant) of 60 milligrams every four to six hours, not to exceed 240 milligrams/day).

[125] As Dr. Graham A. Patrick, Ph.D., R.Ph., noted in his summary conclusions regarding a public meeting on the safety of dietary supplements containing ephedrine alkaloids, "[I]t has been suggested that the rate of absorption of ephedrine alkaloids in herbal preparations is slower, which may lead to a lower incidence of acute adverse effects, but this hypothesis has not been adequately tested." *See* Graham A. Patrick, Ph.D., R.Ph., Public Meeting on the Safety of Dietary Supplements Containing Ephedrine Alkaloids: Summary Conclusions, Aug. 9, 2000 (hereinafter, "Patrick Summary").

[126] In fact, the Daly study, noted above, noted that "both caffeine and ephedrine have a similar constellation of side effects, which are dose related, and which appear to diminish over time." *See* Daly, *et al.* (Attachment 14).

ingestion of caffeine with such products. In fact, one can only assume that individuals with bronchial asthma who use ephedrine-containing OTC drug products routinely ingest caffeine-containing products such as coffee, tea, and soft drinks.

Common beverages, such as coffee, tea, and cola contain as much, if not more, caffeine than ephedra dietary supplements. A single capsule of a typical ephedra dietary supplement (such as Metabolife 356®), for example, contains only approximately 40 mg of caffeine. In fact, we understand that the caffeine content in one capsule of Metabolife 356® is virtually identical to that of a typical can of cola. Moreover, the maximum recommended intake of Metabolife 356® is 8 capsules per day, which contain 320 mg of caffeine. We understand 320 mg of caffeine is only slightly higher than the amount of caffeine in an average 16-ounce cup of coffee, which many adults consume on the way to work each morning. Therefore, an adult who has a 16-ounce cup of coffee in the morning and a can of cola at lunch may have consumed more caffeine than the caffeine contained in the maximum intake of Metabolife 356® per day.

Medline Plus, a health information service of the National Institutes of Health and U.S. National Library of Medicine, indicates: "Moderate caffeine intake, however, is not associated with any health risk. Three 8 oz. cups of coffee (250 milligrams of caffeine) per day is considered an average or moderate amount of caffeine."[127] In fact, it is generally recognized that the *average* American consumes approximately 200 mg of caffeine each day[128] – so one can reasonably conclude that a significant percentage of the population ingests significantly higher levels. Again, to our knowledge, there is no evidence of ingestion of products containing caffeine in combination with OTC drugs containing ephedrine posing any safety problems. In fact, RAND reviewed 52 clinical trials, many of which involved combinations of caffeine and ephedrine alkaloids, and did not identify a single adverse event resulting from the combination.

It is our understanding that FDA's only stated concern regarding caffeine/ephedrine alkaloid combinations in OTC drug products has been misuse – not the safety of such products under normal conditions of use. FDA has issued an Advisory Opinion and an amended Advisory Opinion, regarding OTC drug products with active ingredients such as caffeine/ephedrine, caffeine/pseudoephedrine, and caffeine/PPA combinations, which are marketed as illicit street drug alternatives.[129] It is our understanding that FDA issued these Advisory Opinions due to

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[127] http://www.nlm.nih.gov/medlineplus/ency/article/002445.htm.

[128] See *Caffeine Report issued by the Center for Science in the Public Interest, available at* http://www.cspinet.org/nah/caffeine/caffeine_corner.htm, citing research conducted by John J. Barone.

[129] *See* 49 Fed. Reg. 26814 (1984); 48 Fed. Reg. 52513 (1983).

concerns regarding the misuse and abuse of such products (*i.e.* in an attempt to get high), *not* the safety of those products under normal conditions of use.

In its Advisory Opinions, FDA recognized that the real problem with street drugs is that they are marketed and promoted as products "capable of producing effects similar to those produced by substances subject to the [Controlled Substances Act]." Because these products are marketed and promoted as illicit street drug alternatives, they themselves are misused and abused. Misuse concerns are entirely distinguishable from safety concerns associated with normal use consistent with use recommendations. Notably, FDA, in its Advisory Opinions, does not claim that merely ingesting OTC drug products that contain caffeine/ephedrine causes health problems. Nor, to our knowledge, does the docket for the Advisory Opinions include studies regarding alleged adverse reactions or adverse events from dietary supplements containing caffeine/ephedrine alkaloid combinations. Although FDA's concerns regarding the potential misuse of OTC drugs that are expressly marketed as illicit street drug alternatives are legitimate, misuse concerns (*i.e.* use to "get high") are distinct from safety concerns.

On September 27, 2001, the FDA issued a Federal Register notice (final rule)[130] indicating that the combination of ephedrine and caffeine is prohibited in bronchodilator drug products. FDA indicated that it was unaware of any such OTC drug bronchodilator combination products being on the market, and we understand that the Agency did not receive any related substantive comments in response to its tentative final monograph (which was issued in 1988). Accordingly, under the OTC Drug Review, it is our understanding that the combination was prohibited based upon the absence of any data submitted to the agency in support of safety/efficacy. FDA's decision to prohibit the combination appears to have been based upon improper marketing and potential misuse and abuse of such products - as opposed to safety concerns.

As explained above, the "unreasonable risk" standard under DSHEA clearly indicates that products must be evaluated based upon product labeling; the failure to follow label directions (i.e. misuse and/or abuse) is a legally suspect factor for FDA to consider when making an "unreasonable risk" assessment. Moreover, as explained herein, the science strongly supports the conclusion that dietary supplements that contain ephedrine, along with caffeine, do not present an unreasonable risk to public health. RAND identified no scientific evidence from controlled clinical trials to conclude that ephedrine and caffeine present any serious risks – and documented the weight loss benefits of such products. Products with proven benefits, and only hypothetical serious risks, do not present an unreasonable risk to health.

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[130] 66 Fed. Reg. 49276 (2001).

5. The Number of Subjects Participating in the Clinical Trials is Sufficient and Consistent with FDA's Science-Based Approach

In its White Paper on ephedra, FDA indicated that RAND's meta-analysis "only has enough statistical power to conclude that the rate of serious adverse events, including acute myocardial infarction, stroke, and death is very likely to be less than 1 in 1000." Specifically, RAND stated

> The strongest evidence for causality should come from clinical trials; however, in most circumstances, such trials do not enroll sufficient numbers of patients to adequately assess the possibility of rare outcomes. Such was the case with our review of ephedrine and ephedra-containing dietary supplements. Even in aggregate, the clinical trials enrolled only enough patients to detect a serious adverse event rate of at least 1.0 per 1,000. For rare outcomes, we reviewed case reports, but a causal relationship between ephedra or ephedrine use and these events cannot be assumed or proven.[131]

The important point to keep in mind is that RAND identified no serious adverse events among the subjects participating in the clinical trials. Based upon our understanding of the RAND Report, RAND appears to have reviewed over 50 clinical trials that included over 1,000 subjects in making its safety-related conclusions. Moreover, despite RAND's contentions, it should be possible, based on studies that are currently available, to detect the normal rate of stroke in the population.

RAND's contention that the sample size of available studies is too small to detect certain serious adverse events presumes that the risks argued to be associated with ephedra are rare disorders which would not be expected to occur in the general population at a rate greater than 1.0 per 1000. We understand, however, that the incidence of heart attack and stroke in the United States, is, in fact, significantly less than the 1 in 1000 RAND focuses on. Accordingly, had use of ephedra/ephedrine in fact been associated with an increased risk of these disorders, the RAND study should have detected it – but it did not. As such, we believe RAND's conclusion should have been that they detected no evidence of such increased risk with use of these products.

DSHEA does not require a precise amount of scientific evidence to support product safety. Rather, DSHEA provides that a dietary supplement may be deemed adulterated only if it

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[131] RAND Report Summary, p 6.

"presents a significant or unreasonable risk of illness or injury under conditions of use recommended or suggested in labeling."[132] Moreover, DSHEA provides that the government bears the burden of proof to show that a dietary supplement is adulterated.[133] This standard is intentionally far more lenient than the statutory standard for drug safety. Congress specifically indicated, in the Findings section of DSHEA, "dietary supplements are safe within a broad range of intake, and safety problems with the supplements are relatively rare."[134] Congress never made this type of statutory finding with regard to drug products approved via the NDA process or marketed under the OTC Drug Review. Accordingly, Congress clearly envisioned a dietary supplement safety standard more akin to conventional food products than drug products.

6. Anecdotal Data May Not Be Used for Causation Analysis in the Instant Case – Even Assuming Under-Reporting

a. Background: Anecdotal Data

FDA has long been aware of the problems associated with use of anecdotal data for causation purposes. We have identified, above, the express statements made by RAND to the effect that case reports are not sufficient to prove causation. As Haller and Benowitz, authors of an oft-cited analysis published in the New England Journal of Medicine, which criticized ephedra-based supplements, acknowledged, the FDA AERs they reviewed do not "prove causation, nor [do they] provide quantitative information with regard to risk."[135]

It is axiomatic that anecdotal data is not sufficient to demonstrate causation in situations where the alleged events occur frequently in the general population. In this regard, it should be recalled that as recently as June 14, 2002, in a letter to Sidney Wolfe, based upon the information available to him at the time, Secretary Thompson of HHS indicated that the "FDA advised [him] that the types of observed outcomes reported in relationship to the ingestion of ephedrine alkaloids are not uncommon in the general population and therefore the reports alone do not provide a

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[132] 21 U.S.C. § 342(f)(1) (Supp. 2000).

[133] *See id.*

[134] *See id.* § 321.

[135] C.A. Haller & N.L. Benowitz, *Correspondence (Author's Reply)*, 344 New England Journal of Medicine 1096 (2001). (*See* Attachment 20). The authors were clarifying their earlier study: C.A. Haller & N.L. Benowitz, *Adverse cardiovascular and central nervous system events associated with dietary supplements containing ephedrine alkaloids*, 343 New England Journal of Medicine 1833 (2000). (*See* Attachment 21).

scientific basis for assessing the safety of ephedrine alkaloids or establish a link between the reported events and the ingestion of ephedrine alkaloids."

In particular, ephedra-containing products are taken primarily for weight loss purposes.[136] In considering FDA's adverse event reports, this background population must be considered. The risk of cardiovascular disease increases among individuals who are over-weight. Anecdotal data indicating adverse events among this population, for this and other reasons stated herein, therefore cannot be read to demonstrate causation.

The conclusion that anecdotal reports cannot be used to demonstrate causation has been reiterated by governmental entities such as the General Accounting Office, Office of Inspector General, and Institute of Medicine. In July 1999, the GAO issued its report on ephedra and concluded that FDA's adverse event reports are unreliable as they are subjective, imprecise, and fail to consider the rate of health problems in the general population (i.e. background rates).

The GAO observed that FDA's AERs are inherently unreliable because such AERs are subjective, imprecise, and fail to consider the following: (1) that professional opinions as to the causation of adverse events may differ when multiple risk factors are involved, (2) that serious adverse events are more likely to be spontaneously reported than less serious events, and therefore underreporting leads to skewed data, (3) that there are biases inherent in spontaneous reporting, (4) an estimation of population exposure, and (5) that the quality of the data received was generally poor.[137] Accordingly, the GAO concluded that the "inherent weaknesses of AERs," and FDA's reliance on them, added uncertainty to FDA's proposed rule.[138]

Similarly, in April, 2001, the HHS Office of Inspector General (OIG) issued a report entitled: "Adverse Event Reporting for Dietary Supplements: An Inadequate Safety Valve." In that report, the OIG indicated that:

> FDA relies on the adverse event reporting system to generate signals of possible public health concerns. When signals are

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[136] As noted, FDA has indicated that such weight-loss claims are appropriate for dietary supplements sold over-the-counter to consumers.

[137] *Dietary Supplements, Uncertainties in Analyses Underlying FDA's Proposed Rule on Ephedrine Alkaloids,* GAO Report to the Chairman and Ranking Minority Member, House Committee on Science, at 35-36 (July 1999) (hereinafter, "GAO Report").

[138] GAO Report, p. 10.

> generated, FDA still needs to assess the signal to determine if a public health problem exists. FDA can investigate the signal in many ways including examining clinical information and/or conducting laboratory tests;[139] and
>
> FDA's adverse event reporting system for dietary supplements generates signals of possible public health risks. As is the case for any database, if the data coming in are poor the analysis coming out will also be poor.[140]

Moreover, RAND emphasized, "[s]cientific studies (not additional case reports) are necessary in order to assess the possible association between consumption of ephedra-containing dietary supplements and these serious adverse events."[141] Based upon the above, the scientific, legal, and regulatory standard is clear. Anecdotal data may not be used for causation analysis when the reported events occur frequently in the general population – which is precisely the situation with regard to ephedra.

b. Under-Reporting Analysis

FDA has repeatedly expressed the concern that anecdotal reports allegedly associated with ephedra ingestion are under-reported, and therefore analyses of such reports significantly under-estimate the alleged risk associated with such products.[142] There is obviously no doubt that not everyone who experiences a significant adverse event in temporal proximity to ingestion of a dietary supplement product reports such an event in a manner that ultimately leads to FDA review. The critical question, however, is the extent to which under-reporting occurs in general – and the extent to which under-reporting occurs in situations (such as the ephedra situation) where the media focuses extensive attention on potential risks associated with the ingredient. The media has, in fact, focused on the alleged risks associated with ephedra for several years, thereby increasing the likelihood of over-reporting, rather than underreporting.

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[139] *Adverse event reporting for dietary supplements: an inadequate safety valve*, Department of Health and Human Services, Office of Inspector General (April 2001) (hereinafter, "OIG Report - Adverse Event Reporting"), p. 2.

[140] OIG Report - Adverse Event Reporting, p. 11.

[141] RAND Report, p. 221.

[142] Determining the percentage of people who report adverse events must be estimated based upon past experience. A number of analyses that address under-reporting in the context of vaccines and physician reporting for adverse drug reactions are not addressed herein.

In FDA's initial 1997 proposed rule for ephedrine alkaloids, FDA estimated that the reporting rate for all adverse events (not just serious events) associated with dietary supplements containing ephedrine alkaloids was 10%.[143] According to FDA:

> Typical reporting rates for passive reporting systems addressed to adverse events associated with drugs are generally assumed to be on the order of 10 percent. Reporting rates are higher than usual if the potential health risks associated with a particular substance are widely publicized, if the adverse events are considered to be otherwise unusual, and if reports are gathered from a variety of sources. On the other hand, reporting rates would be lower than usual if consumers and physicians assume that dietary supplements are incapable of producing adverse events because they are not drugs or because they are "natural." In order to incorporate this uncertainty, the reporting rate for the relevant adverse events [for dietary supplements that contain ephedrine alkaloids] is assumed to be 10 percent.[144]

Subsequently, the GAO, in its critique of FDA's proposed rule on ephedrine alkaloids, did not critique FDA's estimate that 10% of all adverse events associated with ephedrine alkaloids are reported, nor did it make an estimate of its own. However, the GAO did cite a 1994 article that indicated that 10% of serious events, and 2-4% of non-serious events, are reported to the British passive surveillance system.[145]

The assumption that only 10% of serious events associated with a dietary supplement are reported is contradicted, however, by a real-world experience involving Eosinophilia-Myalgia Syndrome ("EMS") and L-Tryptophan. In an Agency report regarding EMS and L-Tryptophan, FDA indicated that the reporting rate to the Centers for Disease Control ("CDC") for cases of EMS, a rare and serious syndrome linked to certain L-Tryptophan dietary supplements, was approximately 50%. [146]

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[143] 62 Fed. Reg. 30677, 30707 (1997).

[144] *Id.* (Emphasis added).

[145] GAO Report, p. 35.

[146] *"Dear Colleague" letter regarding the research on Eosinophilia-Myalgia Syndrome and current regulatory status of L-Tryptophan*, FDA Office of Health Affairs (Sept. 3, 1992), *available at* http://www.cfsan.fda.gov/~dms/ds-ltr3.html (hereinafter, "Dear Colleague Letter").

Despite the above, the Office of Inspector General ("IG"), Department of Health and Human Services recently issued a report that referred to a literature review concerning reporting rates, which was commissioned by FDA and conducted by Dr. Alexander Walker from the Harvard School of Public Health (the "Walker Review").[147] According to the Walker Review, FDA receives "less than 1 percent" of adverse events associated with dietary supplements in general.[148] Importantly, however, it is our understanding that Dr. Walker did not estimate a reporting rate for serious adverse events associated with dietary supplements that contain ephedrine alkaloids.

In this instant case, there is no denying that ephedra has been a primary focus of FDA activity and media scrutiny during the past seven years. Since 1995, and in particular since 1997, thousands of television and print stories on ephedra have appeared on a routine basis. Based upon this level of scrutiny and attention, it would seem logical to assume that reporting of alleged adverse events temporally related to ephedra would be at the higher level of the above-mentioned ranges. Moreover, reporting of "serious" events (such as heart attack, stroke, and seizure) would likely be even higher than less serious events. It would also seem logical to assume that it is more likely that over-reporting of events may have occurred in certain instances based upon media attention and potential solicitation of clients by trial attorneys.

Based upon the above, it would appear reasonable to assume that if under-reporting occurred, such under-reporting may range from 10% to 50%. We note that FDA itself assumed a 10% reporting rate in its 1997 proposed rule regarding ephedrine alkaloids, but that FDA's EMS/L-Tryptophan report may be particularly relevant to the instant case because it involved a dietary supplement product that, like ephedrine alkaloids, had been the subject of significant publicity.

c. Aspirin, Acetaminophen, Aspartame, and Feldene Examples

As noted, FDA has repeatedly acknowledged that anecdotal data is not sufficient to establish causation when the reported types of adverse events occur frequently in the general population. FDA's White Paper, for example, provides: "Thus, as has marked the history of inquiries into ephedra's safety, further analysis of safety risks involves case reports - the weakest form of epidemiological evidence since there are no direct 'controls' for any confounding factors or even for the natural occurrence rate of these serious events."

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[147] OIG Report - Adverse Event Reporting.

[148] OIG Report – Adverse Event Reporting, p. 9.

There is substantial Agency precedent for reviewing anecdotal data from a scientific perspective, and for not assuming causation based simply on case reports. For example, in 2000, alone, the American Association of Poison Control Centers ("AAPCC") received 16,649 calls regarding exposure, or potential exposure, to aspirin, and 56,731 calls regarding exposure, or potential exposure, to acetaminophen.[149] After collecting follow-up information on approximately 44% of those calls, the poison control center determined that of the adverse events followed in the year 2000, at least 5,946 adverse events (including 52 deaths) were plausibly related to aspirin and at least 9,660 adverse events (including 99 deaths) were plausibly related to acetaminophen.[150]

In 1986, the Community Nutrition Institute ("CNI") filed a petition with the HHS seeking an immediate ban of aspartame, pursuant to an "imminent hazard" provision, which claimed that aspartame causes neurological damage (*e.g.*, seizures) or eye damage in a significant portion of consumers.[151] To support that claim, CNI relied primarily on anecdotal data concerning epileptic seizures and eye damage, including over 3,000 reports allegedly associated with aspartame collected by FDA over a two year period, a review of a portion of the FDA AERs conducted by the Centers for Disease Control ("CDC"), letters and case reports collected by several physicians, and even an animal study.

However, HHS concluded that this information was insufficient to establish that an "imminent hazard" was present, explaining that "[t]he evidence submitted [by the petitioners] is not of the type that, standing in and of itself, establishes a link between aspartame consumption and possible harm to public health."[152] HHS further explained that the type of information presented was insufficient to "materially affect the scientific determination that aspartame has been shown to be safe for its approved uses,"[153] because the information was not "reliable or concrete."[154]

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[149] *See* Toby L. Litovitz, M.D., *2000 Annual Report of the American Association of Poison Control Centers Toxic Exposure Surveillance System*, 19 The American Journal of Emergency Medicine 337 (Sept. 2001).

[150] *Id.* The adverse effect numbers listed represent the aggregate number of minor, moderate, and major effects, and deaths reported by the AAPCC.

[151] *November 21, 1986 Health and Human Services Letter Denying Aspartame Imminent Hazard Petition*, p.8 (hereinafter, "HHS Aspartame Petition Denial").

[152] HHS Aspartame Petition Denial, at 2. *See also FDA's Recommendation Regarding Disposition of Imminent Hazard Petition Regarding Feldene (piroxicam) – Decision,* (May 27, 1986) (hereinafter, "FDA Feldene Recommendation"), at 5 (recommending the denial of a petition seeking to ban Feldene for use in people over the age of 60. HHS noted that the reports collected over a four year period, in addition to theoretical pharmacokinetic evidence, failed to provide any evidence that the drug presented an "imminent hazard"), *aff'd* Letter from Health and Human Services Secretary Bowen to Sidney Wolfe (July 7, 1986) (hereinafter, "HHS Feldene Petition Denial").

[153] *See* HHS Aspartame Petition Denial, at 8.

In reaching the conclusion that the above information did not suggest a causal relationship between aspartame and seizures, HHS noted that the FDA AERs "showed no consistent association between the occurrence of seizure and exposure to aspartame containing products."[155] Moreover, HHS noted that in reviewing the anecdotal reports and available medical records, FDA was "unable to eliminate factors other than aspartame consumption as possible causes of reported seizures," given that "[s]eizure susceptibility can be increased by a number of factors, such as estrogenic activity, insulin deficiency, hydration, hyponatremia, and starvation."[156]

HHS also acknowledged that the anecdotal records in and of themselves could not establish a causal relationship between aspartame and seizures, given the high rate of seizures in the general population:

> Approximately one percent of the population suffers from seizures. Epilepsy is second only to stroke as the leading neurological disorder in the United States. Under these circumstances and, because aspartame is frequently consumed by large numbers of people, it is not surprising that there may be a chance occurrence of seizure activity following ingestion of aspartame in seizure prone people. . . . In fact, such a happenstance would not be unexpected.[157]

HHS acknowledged that reports, and other forms of anecdotal evidence, could not even establish a hypersensitivity towards aspartame in certain populations because the symptoms attributed to aspartame were of "a common nature" (*e.g.*, headache).[158] According to HHS, the recommendations of the CDC from its analysis of the reports, and an FDA guidance document,[159] only scientific evidence from well-controlled clinical trials focusing on specific endpoints could establish hypersensitivity to a product.[160]

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[154] *See id.*

[155] *See id.* at 3.

[156] *See id.* at 4. (emphasis added).

[157] *Id.* at 4.

[158] *See id.* at 4-5.

[159] *See* Findings of FDA's Advisory Committee on Hypersensitivity to Food Constituents (May 9, 1986).

[160] *See generally* HHS Aspartame Petition Denial.

Furthermore, HHS dismissed claims that the reports received by FDA relating to eye damage had any causal relationship to aspartame, noting that (1) the majority of the cases were more likely caused by underlying disease or concurrent drug use, and (2) many of the reports could not be properly analyzed because of insufficient or absent medical records.[161] HHS also determined that toxicological/pharmacological evidence showing that methyl alcohol at high levels could adversely affect the eyes, was insufficient to demonstrate that aspartame presented an "imminent hazard" because methyl alcohol is present in aspartame only at low levels.[162] Finally, HHS also rejected the petitioner's presentation of an animal study, which allegedly suggested that aspartame may cause eye damage. According to HHS, that study was merely preliminary, and insufficient to link aspartame to eye damage because it was an animal study with multiple design deficiencies.[163]

HHS' denial of Public Citizen's 1986 petition seeking to ban the use of Feldene in people over the age of 60 provides another example of HHS' steadfast refusal to find that an "imminent hazard" is present based merely upon anecdotal data - particularly when such evidence is contradicted by well-controlled clinical studies.[164] In that case, to support its petition, Public Citizen presented, among other things, 2,803 anecdotal reports (182 of which involved fatalities) collected by FDA over a two-year period. In denying the petition, HHS discounted the large number of reports associated with Feldene, in part, because of over-reporting (FDA estimated that the reporting rate for adverse events allegedly associated with Feldene was approximately 1.65 times the rate expected).[165]

The above examples are particularly instructive, and relevant, to the situation regarding ephedra. If anecdotal reports refer to situations where rare side effects are temporally associated with ingestion of a product, it may be possible after conducting statistical analyses to conclude with some degree of assurance that a causal link exists. With regard to ephedra, however, the reported anecdotal side effects are widespread in the general population – as was the case with aspirin,

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[161] *See generally id.* at 5-6.

[162] See *id.* at 6.

[163] *See id.* at 6 (footnote 6).

[164] *See generally* FDA Feldene Recommendation, *aff'd* HHS Feldene Petition Denial.

[165] *See* FDA Feldene Recommendation at 4-5, *aff'd* HHS Petition Denial. Notably, although the FDA Feldene Recommendation does not explain how FDA arrived at its estimate of the reporting rate, it does state that it is adjusting the numbers because of an observed trend in adverse event reporting for all drugs and because all drugs have increased reporting rates in the first three years in which they are marketed. *See id.*

aspartame, acetaminophen, and Feldene®. As noted by HHS in the aspartame review, background rates of side effects in the general population may not be ignored – as chance occurrences are to be expected. Accordingly, due to the absence of any clinical data demonstrating serious side effects associated with dietary supplements that contain ephedrine alkaloids, there is no scientific rationale to conclude that the types of reported anecdotal side effects amount to anything more than background noise from the general population.

7. The Mild to Moderate Side Effects Identified by RAND Are Consistent with OTC Products Approved for Marketing by the FDA, and FDA Has Been Aware of These Types of Effects Since At Least 1976

RAND identified four types of non-serious adverse events associated with ephedrine alkaloids: (1) psychiatric symptoms such as anxiety and change in mood; (2) autonomic hyperactivity; (3) nausea/vomiting; and (4) palpitations. RAND concluded that ephedrine/caffeine is associated with two to three times the risk of the above events.

FDA, in its Ephedra White Paper, referred to the above events as "mild to moderate" side effects. This is not surprising, as the above events are basically consistent with the types of events that may be experienced upon ingestion of caffeine alone. FDA's OTC Drug Review, for example, mandates that caffeine-containing stimulant drug products contain a warning indicating that too much caffeine may cause "nervousness, irritability, sleeplessness, and occasionally, rapid heart beat."

More importantly, FDA has been aware for many years of the potential for ephedrine to produce mild to moderate side effects. In fact, FDA's OTC Drug Monograph for ephedrine-containing bronchodilators mandates a warning regarding "nervousness, tremor, sleeplessness, nausea, and loss of appetite." Under the OTC Drug Review, FDA's own advisory panel made the following statements regarding ephedrine in 1976:

> a. *Ephedrine preparations (ephedrine, ephedrine hydrochloride, ephedrine sulfate, racephedrine hydrochloride).* The Panel concludes that ephedrine preparations are safe and effective for OTC use as bronchodilators as specified in the dosage section discussed below.

> (1) *Safety.* Ephedrine, when absorbed systematically, has effects both on the brain (central) and on nerve endings (peripheral) (Ref. 1). In clinical usage, the central effects are stimulatory and include tenseness, nervousness, tremor and sleeplessness. Peripheral effects include bronchodilation, and possibly shrinkage of mucous membranes (decongestion), although this has not been documented. Other peripheral effects include awareness of heartbeat and rapid heat beat accompanied usually by some elevation of blood pressure. However, a study by Dulfano and Glass on 26 asthmatics between the ages of 28 and 61 years showed that a single dose of 25 mg had no significant effect on either heart rate or blood pressure (Ref. 2). Another recent study of the cardiovascular effects of 25 mg ephedrine in 20 asthmatics showed there was only a modest increase in heart rate up to 11 beats per minute as a maximum, and the systolic and diastolic blood pressure showed no significant change (Ref. 3). In spite of these findings, the cardiovascular and central effects appear to set limits on dosage, limits which vary widely among patients as judged by clinical experience. Loss of appetite and nausea also occur in some patients. Difficulty in urination may occur in older males who might have enlarged prostate glands. The drug, under these circumstances, exacerbates obstruction to urine flow by causing spasm of the outlet of the bladder. Over-dosage results in exaggeration of the side effects which patients describe as disagreeable and can usually be depended upon to prevent overuse or abuse. Ordinary doses may cause marked and potential dangerous increase in blood pressure in patients taking drugs, containing monoamine oxidase (MAO) inhibitors.[166]

The four types of mild to moderate side effects identified by RAND clearly do not pose an unreasonable risk to health. If FDA were concerned about these types of adverse events, it would be obligated to challenge the marketing of many OTC drug products currently approved for marketing by the Agency. Moreover, if FDA were particularly concerned about these types of events, the extensive review and analysis associated with ephedra over the past eight years has been entirely unnecessary – as FDA has long been aware of these types of potential issues, and warnings should be sufficient to address these types of concerns.

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[166] 41 Fed.Reg. 38370-71 (1976) (emphasis added).

a. Expert Analyses[167]

According to Dr. Graham A. Patrick, Ph.D., R.Ph., who conducted a review of FDA AERs to address the scientific inadequacies associated with FDA's 1997 proposed rule, the extent to which side effects occur when ephedrine is taken as directed, alone or in combination with caffeine, are not much greater in magnitude than the side effects of caffeine in quantities that may be consumed in dietary beverages or in OTC drug caffeine preparations.[168] Moreover, Dr. Robert M. Stark, a cardiologist, has observed that the overall health risk associated with ephedrine alkaloids at the recommended dosages, even when combined with caffeine, is far less, than that associated with ingestion of peanut products by the general population, a small percentage of whom have peanut allergies.[169]

In addition, Dr. Arne Astrup has clarified that the caffeine/ephedrine combination actually does not have negative "synergistic" effects:

> According to the definition, *Synergism*, is an additive, or greater than additive, effect . . . . Whereas studies show there is evidence of a synergistic effect of ephedrine and methylxanthines with respect to thermogenic and bronchodilator actions, there is no evidence to support Dr. Love's statement that adverse effects of the two agents are synergistic. Rather, there is substantial evidence that . . . combining E+C [ephedrine and caffeine] does not increase the severity and likelihood of adverse events. . . .[170]

Dr. Astrup went on to note, "In fact, we found . . . that there was a positive effect of combining ephedrine and caffeine on heart rate because caffeine tends to abolish the slight increase in heart rate that was observed in patients taking ephedrine alone."[171]

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[167] The analyses discussed in this section were conducted well prior to FDA's recent reopening of the comment period and therefore did not take into consideration recent data and information available to the Agency.

[168] Patrick Summary.

[169] Letter from Robert M. Stark, M.D., F.A.C.P., F.A.C.C., to the Office on Women's Health, dated Aug. 8, 2000 (hereinafter, "Stark Summary"), at 3.

[170] Arne Astrup, M.D., Ph.D., *Commentary on Lori A. Love's "Evaluation of the Safety of Food Products Containing Ephedrine Alkaloids,"* at 1-2. (hereinafter, "Astrup Commentary").

[171] Astrup Commentary, p. 3.

Moreover, as explained previously, some experts have indicated that taking herbal ephedra, rather than synthetic ephedrine, may actually result in even fewer adverse side effects because the other alkaloids in herbal ephedra, such as pseudoephedrine, are less potent than the ephedrine alkaloid.[172] These experts indicate that herbal ephedra, on a mg per mg basis, is likely to be safer than synthetic ephedrine in OTC drugs (which FDA found to be "generally recognized as safe and effective" for their intended use).[173]

Finally, Dr. Patrick noted that the risk of experiencing adverse events from using dietary supplements containing ephedra should not increase with long-term use.[174] Absorption of ephedrine begins within minutes after ingestion, and the peak concentration in the plasma is obtained within 1 to 2 hours.[175] The half-life of ephedrine ranges from 4-6 hours.[176] Because the maximum accumulation, the plateau level, of a compound is generally achieved within 5 to 7 half-lives, ephedrine reaches its maximum level in the blood between 1 and 4 days of taking it on a regular schedule. There is no increased accumulation of ephedrine in the plasma beyond that, even though dosing continues at a steady rate.[177] Accordingly, the level of ephedrine in the plasma after 7 days of taking ephedrine regularly, or 90 days for that matter, cannot be higher than the level of ephedrine in plasma after taking ephedrine for 1-4 days. Moreover, in clinical studies individuals have consumed ephedra for as long as 26 months without reported serious adverse effects. Accordingly, there is little or no scientific evidence that duration of exposure to ephedra products, when taken in recommended doses, is related to any incidence of serious adverse events.

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[172] *See* Patrick Summary.

[173] *See* Patrick Summary; see also G.R. Kaats & J.A. Adelman, *Effects of a Multiple Herbal Formulation on Body Composition, Blood Chemistry, Vital Signs, and Self-Reported Energy Levels and Appetite Control*, 18 (1 Supp.) International Journal of Obesity and Related Metabolic Disorders 145 (June 1994) (concluding that herbal ephedra is efficacious for weight loss without any of the mild and transient side effects that sometimes occur with ephedrine).

[174] *See* Patrick Summary.

[175] *See* Graham A. Patrick, Ph.D., R.Ph., Preliminary Commentary on Food and Drug Administration Proposed Rule in Limitations on Dietary Supplements Containing Ephedrine Alkaloids, 1997 (hereinafter "Patrick Commentary"), p.2.

[176] *See* Patrick Commentary., p.2 See also Goodman & Gilman *et al.*, *The Pharmacological Basis of Therapeutics* (9th ed 1996), at 221.

[177] *See* Patrick Commentary, pp. 2-3.

In conclusion, the adverse side-effects that have been observed in the clinical studies of herbal ephedrine alkaloids or synthetic ephedrine, alone or in combination with caffeine, have been transient and mild. As noted, experts have commented that these side-effects "are not much greater in magnitude than the side-effects of caffeine [alone], in quantities that may be consumed in dietary beverages or in [over-the-counter ("OTC")] preparations."[178] And, as noted above, RAND reviewed 52 clinical studies, many of which involved combinations of ephedrine and caffeine, and did not identify any serious adverse events related to the combination. Finally, even FDA has stated that synthetic ephedrine is "generally recognized as safe and effective" ("GRASE") at dosages of 150 mg/day in OTC drug products such as asthma remedies.[179] Therefore, the combination of ephedra with caffeine in dietary supplement products is entirely appropriate.

b. Many FDA-Approved OTC Drug Monographs Contains Similar if Not Identical Warnings

FDA has clearly indicated that over-the-counter drug products widely available to the public may produce mild to moderate side effects such as those identified by RAND and still be generally recognized as safe and effective under FDA's OTC drug review. The following FDA regulations (OTC drug monographs), for example, all mandate warnings for side effects similar or identical to those allegedly associated with ephedra:

> **21 C.F.R. §340.50 - Stimulant Drug Products for over-the-counter human use.**
>
> "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 heartbeat."

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[178] *See* Patrick Summary.

[179] 51 Fed. Reg. 35326, 35331 (1986).

21 C.F.R. §341.80 - Labeling of Nasal Decongestant Drug Products.

"If nervousness, dizziness, or sleeplessness occur, discontinue use and consult a doctor."

21 C.F.R. §343.80 - Professional Labeling of Internal Analgesic Antipyretic and Antirheumatic Drug Products for Over-the Counter Human Use.

"GI Side Effects: GI side effects include stomach pain, heartburn, nausea, vomiting, and gross GI bleeding. Although minor upper GI symptoms, such as dyspepsia, are common and can occur anytime during therapy, physicians should remain alert for signs of ulceration and bleeding, even in the absence of previous GI symptoms. Physicians should inform patients about the signs and symptoms of GI side effects and what steps to take if they occur."

21 C.F.R. §346.50 Labeling of Anorectal Drug Products.

For products containing ephedrine sulfate identified in §346.12(a), "Some users of this product may experience nervousness, tremor, sleeplessness, nausea, and loss of appetite. If these symptoms persist or become worse, consult your doctor."

21 C.F.R. §357.150 Labeling of Anthelmintic Drug Products.

"Abdominal cramps, nausea, vomiting, diarrhea, headache or dizziness sometimes occur after taking this drug. If any of these conditions persist consult a doctor."

The existence of the above OTC Drug Monographs, and the fact that OTC drug products have been marketed under such monographs for years, strongly supports the position that the mild to moderate types of side effects identified by RAND are common and do not present a significant or unreasonable risk to public health. Moreover, as noted, the public can be adequately protected from these mild effects through the use of warning labels.

In conclusion, the safety profile of ephedrine/caffeine has been documented in numerous scientific studies and analyses. In its recently issued report on ephedra, RAND indicated that it identified no serious adverse events in the 52 clinical trials regarding ephedrine that it reviewed. Moreover, ephedrine-containing OTC drug products have been marketed for years, at daily levels significantly higher than those provided by dietary supplements containing ephedrine alkaloids, and FDA has indicated that such products have not been associated with serious adverse events. Finally, RAND has acknowledged that anecdotal data in the instant case is not sufficient to prove that ephedra causes serious adverse events. RAND expressly indicated that scientific studies – not additional case reports – are necessary in order to assess the possible association between consumption of ephedra-containing dietary supplements and serious adverse events.

Metabolife supports the recommendation for additional research, and also supports RAND's conclusion that additional case reports are not sufficient to demonstrate potential causation. Products with proven benefits – and only hypothetical serious risks – do not present an unreasonable risk to health.

C. In Determining Whether Products Pose an "Unreasonable Risk," FDA Must Not Treat Disparate Products Identically

A fundamental flaw associated with a review of anecdotal data is the assumption that all ephedra-containing dietary supplements have identical levels of constituents.[180] In fact, in FDA's recent proposed rule for dietary supplement GMPs, the Agency acknowledged that the content of some dietary supplement products containing ephedrine alkaloids varied considerably from the labeled content. Specifically, the proposed rule provides:

> A study found that dietary ingredient content varied considerably from the declared content (Ref. 33). The study examined ephedra alkaloids in 20 herbal dietary supplements containing ephedra (Ma Huang) to determine their ephedra alkaloid content. This study found that norpseudoephedrine was often present in the ephedra dietary supplements. The study also observed significant lot-to-lot variations in alkaloid content for four products, including one product that had lot-to-lot variations of ephedrine, pseudoephedrine, and methylephedride that exceeded 180 percent, 250 percent, and 1,000 percent, respectively. Half of the products

[180] We also note that pharmacologically significant formulation differences could also potentially distinguish one product from another.

> tested differed in their label claims for ephedra alkaloid content and their actual alkaloid content. In some cases, the discrepancy exceeded 20 percent. One product did not have any ephedra alkaloids. Lot-to-lot variation in dietary ingredients is a public health problem particularly because conditions of use recommended or suggested in the labeling of dietary supplements are presumably based on the dietary supplement containing a certain amount of the dietary ingredient. If the dietary supplement contains more or less than the amount that the manufacturer represents, then the consumer does not receive the potential health benefit from the dietary supplement or is exposed to an amount that could present risk of injury or illness.[181]

Based upon the above, and FDA's delay in issuing dietary supplement GMPs (which may be essential in ensuring that products contain what they claim to contain), even if contrary to established scientific principles one were to assume that a specific adverse event could be found to be associated with appropriate supplement ingestion (as opposed to abuse or misuse), those particular events may be the result of a supplement containing an excessive level of ephedrine. In other words, the consumer may have ingested higher levels of ephedrine than appropriately manufactured competing products.

Accordingly, even if FDA were to *assume* that specific adverse events were associated with specific products, there would be no legal, regulatory, or scientific rationale to extend that conclusion to other products. The applicable product may not have been formulated under precise GMPs, and therefore may in fact contain more ephedrine alkaloids than the product was claimed to contain.

Importantly, we note that for years, Metabolife has been at the forefront of developing and employing stringent GMP processes to ensure that its products contain what they claim to contain. For those manufacturers who apply stringent GMP practices, it would be unfair and inappropriate for FDA to classify their products as "unreasonable risks" based upon the hypothetical failings of other companies to currently meet GMPs and produce products with appropriate levels of ingredients.

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[181] 68 Fed. Reg. 12157, 12162-63 (2003).

D. Ephedra, With or Without Caffeine, Does Not Present an Unreasonable Risk when Used as Directed

As demonstrated above, it would be contrary to DSHEA, and the current state of the science, for FDA to conclude that dietary supplements that contain ephedrine alkaloids pose an "unreasonable risk of illness or injury under conditions of use recommended or suggested in labeling." Ephedra has scientifically documented benefits and only hypothetical significant risks. A determination, therefore, that ephedra poses an "unreasonable risk" would be contrary to scientific principles and extensive regulatory precedent.

With regard to efficacy, the scientific evidence – as evaluated by RAND – clearly indicates that the weight loss generated by such ephedra/caffeine-containing supplements is approximately two pounds per month greater than with placebo – for up to six months (three months longer than that recommended by FDA's own Advisory Review Panel for weight loss under the OTC Drug Review).

From a safety perspective, RAND concluded that not a single serious adverse event was reported in any of the 52 clinical trials it reviewed as part of its analysis. All of the well-controlled clinical trials support product safety, and RAND acknowledged that anecdotal data is not sufficient to prove causation. Moreover, it is conceivable that some of the anecdotal reports may reflect product abuse or misuse. At present, therefore, the science unequivocally supports product safety.

Safety is also demonstrated by an assessment of OTC drug products marketed under FDA's OTC Drug Review. As noted herein, the agency has already determined that ephedrine in OTC bronchodilator drugs is generally recognized as safe – with no duration on use - at daily dosage levels higher than ephedra-containing dietary supplements.

As noted previously, according to DSHEA, FDA must determine whether a dietary supplement presents a "significant or unreasonable risk of illness or injury under conditions of use recommended or suggested in labeling." Section 4 of DSHEA (emphasis added). The Congressional directive is clear – potential product abuse and/or misuse is not an appropriate scientific factor to consider when evaluating a dietary supplement under the "unreasonable risk" standard. The statutory language clearly does not permit FDA to evaluate a product under the assumption that conditions of use recommended or suggested in labeling are ignored.

Congress has also correctly concluded that consumers can read product labels and follow directions – and that dietary supplement safety assessments must be conducted based upon this directive. Safety assessments are not conducted in the abstract, and FDA must evaluate product

labeling and apply the "unreasonable risk" standard in light of this conclusion. Any product can be abused or misused, and it would be inappropriate and contrary to the Congressional mandate under DSHEA for the agency to classify a product as an "unreasonable risk" based upon inappropriate product usage.

American consumers deserve the right to choose products that can support their weight loss objectives in a cost-effective manner, and Americans are more than capable of reading and following label instructions and warnings.[182] In fact, a recent study shows that almost 70% of adults read the label every time that they use a product.[183] It is therefore clear that where a sufficient warning label is provided, consumers must be expected to read and follow it, and manufacturers should not be liable for consumers' failure to do so.[184]

Dietary supplements that contain ephedrine alkaloids bear some of the most extensive indications for use and warning labels of any over-the-counter products sold in the United States. The vast majority of ephedra-containing dietary supplements bear labeling that:

* Contains dosage limits
* Prohibits use by minors
* Warns against use by pregnant or nursing mothers
* Advises consumers to first contact a physician prior to use if a consumer has a wide range of health conditions.

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[182] We reiterated, as noted above, that a warning label similar, if not identical, to that on Metabolife 356® obtained a favorable review from the Department of Health and Human Services, Office of Inspector General, who concluded that it was preferred by interviewees because it was complete and addressed such topics as contraindications, interactions, maximum dosage and adverse effects. Such a label, as in the case of OTC drugs, has the ability to reduce the risk to consumers of any adverse effects.

[183] *See Safety of Dietary Supplements Containing Ephedrine Alkaloids,* Report of Public Meeting, Submitted by Wanda K. Jones, Dr. P.H., Deputy Assistant Secretary for Health (Women's Health), Director, Office of Women's Health (Aug. 8-9, 2000).

[184] See e.g., Restatement (Second) of Torts § 402A, which indicates that strict liability will not apply where a consumer has failed to follow a sufficient warning provided by the manufacturer: "Where warning is given, the seller may reasonably assume that it will be read and heeded; and a product bearing such a warning, which is safe for use if it is followed, is not in defective condition, nor is it unreasonably dangerous."

FDA's "unreasonable risk" analysis must take into account such warnings and indications for use. As explained herein, when taken and used appropriately, the safety record of such products appears to be as good as or better than many common OTC drug products.[185]

In conclusion, if a dietary supplement has a proven benefit, and only hypothetical risks, declaring such a product to be unsafe (i.e. an "unreasonable risk") would be in defiance of scientific principles and would be contrary to the Congressional mandate established in DSHEA. FDA has repeatedly acknowledged, including in comments to the Office of Management and Budget ("OMB"), that its regulations must be "science-based." FDA has also repeatedly indicated that well-controlled clinical trials are the best type of scientific data – and anecdotal data (case reports) are insufficient for most scientific purposes.

With regard to ephedra/caffeine efficacy, RAND concluded that upon review of numerous clinical studies, the evidence supports the efficacy of ephedra or ephedra/caffeine for weight loss purposes over a six-month period (three months longer than the weight loss study recommended by FDA's own Advisory Review Panel under the OTC Drug Review) – resulting in weight loss of two pounds per month more than placebo. Adding caffeine to ephedrine resulted in a statistically significant increase in the amount of weight loss.

With regard to safety, FDA, RAND, and the NIH Working Group have all indicated that the scientific clinical evidence is not sufficient to conclude that ephedra causes serious adverse events. RAND concluded that no serious adverse events (e.g. death, myocardial infarction, stroke, etc.) were reported in 52 clinical trials that were reviewed. Moreover, in its White Paper

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[185] In addition, we note that the combination of ephedra with caffeine does not pose an "unreasonable risk" and in fact has been found to provide a proven benefit, when used as directed. As noted above, studies by Dr. Arne Astrup demonstrate that ephedrine in combination with caffeine has an additive thermogenic effect, which makes the combination much more efficacious in supporting weight loss than ephedrine alone. Specifically, in a large study, involving 180 obese subjects on a restricted diet, Dr. Astrup found that an ephedrine/caffeine combination (20 mg./200 mg) resulted in significantly greater weight loss than placebo. Subjects treated with this combination three times per day for 24 weeks (in conjunction with a restricted caloric diet), lost an average of 17.5% of their body weight, compared to a loss of about 14 % for placebo. *See* Toubro and Astrup (Attachment 15). Moreover, Dr. Astrup concluded that "there is no evidence to support [the] statement that adverse effects of the two agents [ephedrine and caffeine] are synergistic. Rather, there is substantial evidence that . . . combining E+C [ephedrine and caffeine] does not increase the severity and likelihood of adverse events." Astrup Commentary, at 1-2. He also noted, "In fact, we found . . . that there was a positive effect of combining ephedrine and caffeine on heart rate because caffeine tends to abolish the slight increase in heart rate that was observed in patients taking ephedrine alone." Astrup Commentary, at 3.

FDA acknowledged that a review of all of the information does "not establish definitive causal evidence of a statistically significant elevated risk of death or serious injury from ephedra."

Finally, FDA is obligated to consider the long-standing marketing, and favorable safety profile, of drug products that contain ephedrine alkaloids under the OTC Drug Review. Such products provide more ephedrine on a daily basis than dietary supplements that contain ephedra, and are routinely ingested along with caffeine. FDA has concluded that such products are "generally recognized as safe and effective" for their intended use. Moreover, these bronchodilator products containing ephedrine do not contain any duration of use limitation. It is unclear what scientific support FDA relies upon in order to theorize that a lower level of ephedrine provided in dietary supplement products may pose a risk to health while it does not do so for OTC bronchodilator drugs.

VI. Use of the OTC Drug Regulatory Model as a Paradigm to Limit Potential Product Abuse/Misuse

Metabolife supports FDA for recently acknowledging the widespread sale of OTC drugs containing ephedrine in the United States and throughout the world. Moreover, in its recently published "White Paper" on ephedra, FDA noted that the OTC drug review can actually provide a model for ephedra regulation:

> However, some additional evidence related to ephedra safety comes from another source: the more restricted availability of synthetic ephedrine in products regulated as drugs, available in low doses and with specific labeling for short-term indications and mandatory warnings, has not been associated with the same magnitude of reported adverse events as ephedra. It seems plausible that a regulatory approach akin to that used for synthetic ephedrine would have a reasonable likelihood of avoiding some of the serious adverse effects that have been reported with ephedra use. Similar restrictions on marketing and access - which could be tightened or loosened depending on further scientific evidence - could provide an effective deterrent to some current practices that appear to exacerbate ephedra's potential risks.[186]

[186] *See* White Paper (emphasis added).

Using the OTC drug regulatory framework as a regulatory model, Metabolife strongly supports a science-based regulatory regime for ephedra-containing dietary supplements whereby strict warning labels, indications for use, dosage limits similar to those in OTC drugs, and GMP compliance are used to ensure product quality and minimize the likelihood of products being abused or misused by consumers. Moreoever, the science-based regulatory regime should reflect the established safety profile of caffeine; RAND, in fact, has indicated that in its review of 52 clinical studies, many of which evaluated the combination of ephedrine alkaloids with caffeine, it has found no clinically significant evidence of an increased risk of serious adverse events.[187]

We believe implementation of such a regulatory regime could limit the sale of products that are currently marketed for uses that could produce abuse or misuse – uses that are clearly distinguishable from weight loss. It is Metabolife's opinion that products marketed as street drugs, or for athletic enhancement or targeted to minors, are more likely to be abused and/or misused by consumers.[188] Metabolife supports FDA for recently initiating enforcement against products marketed as "street drug alternatives." Specifically, on March 31, 2003, FDA sent warning letters to eight companies and individuals marketing ephedra-containing products as alternatives to street drugs.[189] Commissioner McClellan correctly asserted: "Illegal street drugs masquerading as dietary supplements have no legitimate place in the U.S. marketplace. These products pose potentially serious risks to minors and others who taken them, without providing any medical benefits. Simply put, they pose an unacceptable risk to public health."[190] These products, however, must be distinguished from legitimate ephedra-containing dietary supplements, which, when used as directed, promote healthy weight loss.

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[187] As noted, RAND also identified an increase in weight-loss efficacy associated with the use of caffeine with ephedrine.

[188] Metabolife believes a claim to provide energy during weight loss or while dieting is entirely distinguishable from a claim to improve athletic performance, or provide an energy jolt. Many consumers who reduce their caloric intake while dieting may feel sluggish and therefore need energy support. In this context, Metabolife believes that providing energy does not promote abuse and/or misuse.

[189] *FDA Acts Against Potentially Risky Products Illegally Marketed as Street Drug Alternatives,* FDA Press Release (Mar. 31, 2003) (hereinafter "FDA Street Drug Press Release"), *available at* http://www.fda.gov/bbs/topics/NEWS/2003/NEW00889.html. Warning letters were sent to: Cherokee Naturals, Woodstock, Ga.; Ecstasy Melrose, Los Angeles; Mark Hurlbut, Glendale, Ariz.; John Hoover, Edinboro, Pa.; Jason Pacey, Peoria, Ill ; Brian Petruzzi, Margate, N.J.; Shaun Roberts, Tampa; Stardust Industries, Northridge, Calif.

[190] FDA Street Drug Press Release.

VII. FDA Does Not Need Additional Legislative Authorities To Regulate Ephedra – DSHEA Provides Ample Authority

Under DSHEA, FDA has extensive regulatory authority over dietary supplement products. DSHEA contains extensive formulation restrictions, claim restrictions, substantiation requirements, and detailed labeling requirements. Products that fail to comply with FDA regulatory requirements issued under DSHEA may be subject to immediate enforcement action – including but not limited to product seizure or injunctive relief.

Moreover, any product for which FDA believes there is a health risk may also be subject to immediate FDA enforcement. As noted previously, if a dietary supplement contains a dietary ingredient that "presents a significant or unreasonable risk of illness or injury under conditions of use recommended or suggested in labeling," FDA may immediately challenge such a product in court. FDA may also initiate judicial action if a dietary supplement is "adulterated" under traditional FDA precepts. Finally, DSHEA also contains an "imminent hazard" provision that enables the Secretary of the Department of Health and Human Services to initiate immediate action against a product that poses an imminent hazard to public health or safety.

As demonstrated above, it is a myth that FDA does not have sufficient authority under DSHEA to regulate dietary supplement products. Contrary to popular belief, dietary supplements are not unregulated. FDA has ample authority to initiate enforcement actions and protect the public under the current statutory framework.

VIII. Preemption of State Labeling Requirements

Metabolife strongly believes that in the event FDA finalizes mandatory labeling requirements for dietary supplement products that contain ephedrine alkaloids, such regulation should expressly preempt state labeling requirements. Based upon the label space needed to comply with FDA's proposed warning label, it would be virtually impossible to include labeling that complies with FDA regulatory requirements along with potentially different requirements in each of the 50 states. In addition, from a substantive perspective, it likely would be confusing and misleading for consumers to read different (and likely contradictory) warnings on such products.

From every perspective, it would be untenable for FDA to mandate such detailed and lengthy warnings, and then to permit states to mandate their own, conflicting detailed warnings. FDA's regulation of this matter should preempt any state regulation of warning labels.

IX. Research Proposal by the National Institutes of Health, National Advisory Council for Complementary and Alternative Medicine (NACCAM) Working Group on Ephedra ("NIH Working Group").

As noted previously, on February 26, 2003, the NIH Working Group recently evaluated the RAND Report, and concluded that the data on ephedra safety is inconclusive – it cannot be demonstrated, based upon current data and information, that ephedra is not safe. On March 17, 2003, the NIH Working Group suggested initiation of multi-site, prospective case-control study to assess the risk associated with taking ephedra.

Although the logistics and details of such a study still need to be reviewed and evaluated, from a conceptual standpoint Metabolife strongly supports the initiation of a prospective case-control study to confirm the safety of dietary supplements that contain ephedrine alkaloids.

X. Conclusion

As demonstrated herein, dietary supplements containing ephedrine alkaloids, and caffeine, provide significant weight loss benefits. RAND concluded, upon review of numerous clinical studies, that the evidence supports the efficacy of ephedrine/caffeine for weight loss purposes over a six-month period – resulting in weight loss of two pounds per month more than placebo. RAND also found that adding caffeine to ephedrine resulted in a statistically significant increase in the amount of weight loss.

The above conclusion cannot be overstated. The Surgeon General has indicated that over-weight and obesity have reached epidemic proportions. An estimated 61 percent of U.S. adults are over-weight or obese, and over-weight and obesity constitute the second leading cause of preventable death, after smoking, resulting in an estimated 300,000 deaths per year at a cost (direct and indirect) that exceeds $100 billion a year. Dietary supplements containing ephedrine alkaloids provide millions of Americans with an over-the-counter option to support their weight loss goals and help them maintain their weight.

With regard to safety, RAND concluded that no serious adverse events (e.g. death, myocardial infarction, stroke, etc.) were reported in 52 clinical trials that it reviewed. Moreover, in FDA's recently published White Paper on Ephedra, entitled: "Evidence On The Safety And Effectiveness Of Ephedra: Implications For Regulation," FDA acknowledged that a review of all of the information does "not establish definitive causal evidence of a statistically significant elevated risk of death or serious injury from ephedra." The mere existence of anecdotal reports does not counter the weight of the scientific evidence.

FDA has indicated that risk assessments must be based on sound science, and should be driven and supported by systematic analyses that maintain integrity and are protected from political and other pressure. FDA also indicated that the Agency, in conducting risk assessments, will use: (a) the best available science and supporting studies conducted in accordance with sound and objective scientific practices, including peer reviewed science and supporting studies when available; and (b) data collected by accepted methods (if reliability of the method and the nature of the decision justify use of the data).

Based upon the above scientific principles, it is clear that products such as ephedrine/caffeine that provide proven benefits – and only hypothetical serious risks – do not present a significant or unreasonable risk to health. The scientific evidence supports the safety and efficacy of such products, and the new "studies" cited by FDA in its recent Federal Register notice are inconclusive and do not alter the scientific analysis.

In conclusion, however, Metabolife wishes to emphasize that it, and responsible members of the dietary supplement industry, have long been supporting the science-based regulation of dietary supplements that contain ephedrine alkaloids. As part of such science-based regulation, Metabolife has long supported the concept of a mandatory warning label. Metabolife, therefore, will not oppose the final adoption of the warning label proposed by the Agency. Finally, Metabolife does not believe there is reason to change the statutory framework established under DSHEA. Metabolife thanks the Agency for the opportunity to provide these comments.

Sincerely,

Daniel A. Kracov
Paul D. Rubin
Counsel to Metabolife

Attachments