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VIA ELECTRONIC MAIL AND PRIORITY MAIL

(www.fdadockets@oc.fda.gov)

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

Re: Dietary Supplements Containing Ephedrine Alkaloids; Reopening of the Comment Period [Docket No. 95N-0304]

Dear Sir or Madam:

On behalf of United Metabolic Research Center, Inc. ("United Metabolic"), the undersigned counsel hereby submit these comments to the docket recently established by the Food and Drug Administration ("FDA" or "Agency") to address the new scientific evidence concerning health risks allegedly related to dietary supplements that contain ephedrine alkaloids.[1] United Metabolic is dedicated to the ethical formulation of dietary supplement products based on sound scientific principles. United Metabolic is the manufacturer of some of the best selling mail order dietary supplement products in the United States. Moreover, United Metabolic manufactures all of its products in compliance with the FDA's good manufacturing practices ("GMPs").

Nevertheless, in proposing the new regulations, the FDA has relied on the findings of an allegedly evidence-based review of all available sources of information on ephedrine alkaloid containing dietary supplements by the RAND Corporation, under contract with the U.S. Department of Health and Human Services (the "RAND Report").[2] However, in actuality, the RAND Report drew its minimal conclusions based almost exclusively on its review of Adverse Event Reports ("AERs"). Moreover, the Agency acknowledged that in reopening the comment period, the purported new evidence comes from "approximately 17,000 adverse event reports."[3] This reliance upon AERs represents a flawed analysis by the FDA when one considers that AERs

[1] The undersigned counsel for United Metabolic obtained confirmation from Anthony Curry of the FDA's Center for Food Safety and Applied Nutrition that the FDA would accept comments regarding the Ephedra Proposal until April 7, 2003. According to Mr. Curry's, the April 7, 2003 represented a modification of the earlier April 4, 2003 deadline. Therefore, this letter is being sent dated April 7, 2003 via electronic mail to www.fdadockets@oc.fda.gov and by federal express overnight service.

[2] Shekelle, P.G., M.L. Hardy, M. Maglione, S.C. Morton, "*Ephedra and Ephedrine for Weight Loss and Athletic Performance Enhancement: Clinical Efficacy and Side Effects*," Agency for Healthcare Research and Quality, AHRQ Publication No. 03-E022.

[3] 68 Fed. Reg. 10417, 10418 (March 5, 2003).

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have uniformly been deemed unreliable by independent third parties as well as by the Agency itself. In fact, the reliance on AERs directly contravenes the conclusions of the General Accounting Office ("GAO").[4] Thus, the Agency has espoused a legally flawed, extra-statutory mechanism whereby an entire class of dietary supplement products would be subject to stringent regulatory controls without credible scientific support.

Accordingly, United Metabolic believes that the Agency's attempt to subject dietary supplements containing ephedrine alkaloids to unprecedented regulatory controls and unreasonable warning labels is fundamentally flawed. First, the Agency's attempt to regulate the entire class of dietary supplements containing ephedrine alkaloids under a single regulation violates the Federal Food, Drug and Cosmetic Act ("FFDCA"),[5] as it involves an extra-statutory mechanism not authorized by Congress. Moreover, United Metabolic believes that based upon the inherent unreliability of AERs, there is no credible scientific support for the FDA's proposed regulations. Thus, the proposed regulations would be found to be "arbitrary and capricious" and in violation of the Administrative Procedure Act ("APA").

Secondly, United Metabolic believes that even if the FDA has authority to regulate based upon AERs, in the instant case, any rulemaking would still be "arbitrary and capricious." The conclusions of the RAND Report simply do not support the level of scientific evidence required in order for the FDA to meet its burden of proof under the Dietary Supplement Health and Education Act of 1994 ("DSHEA").[6] Under DSHEA, the FDA is only allowed to prohibit the sale of a dietary supplement if it can show that such dietary supplements present a:

> significant or unreasonable risk of illness under conditions of use recommended or suggested in labeling, or if no conditions of use are suggested or recommended in the labeling, under ordinary conditions of use.[7]

As discussed more fully herein, the RAND Report conceded that a causal relationship between the use of ephedra or ephedrine products and any serious adverse events could not be "assumed or proven."[8] According to the RAND Report:

> case report reviews involve considerably more subjective interpretation than do reviews of randomized trials. Because our goal in this evidence report is to report

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[4] *See* GAO Report: *Uncertainties in Analyses Underlying FDA's Proposed Rule on Ephedrine Alkaloids*, (July 1999).

[5] 21 U.S.C.A. §§ 321-97 (2003).

[6] P.L. 103-417, 21 U.S.C.A. §§ 342(f).

[7] 21 U.S.C.A. § 321(f)(1)(A). (Emphasis added).

[8] *Supra*, note 2 at xvi. (Emphasis added).

> the evidence as objectively as possible, we ceased to assign assessments of causality to the case reports.[9]

Therefore, without the necessary scientific proof to justify the FDA's proposed rulemaking, any attempt to do so would be found by a court to be "arbitrary and capricious" and in violation of the APA. In light of the arbitrary and capricious nature of the proposed rulemaking, United Metabolic respectfully requests that the Agency immediately withdraw all of the provisions in its proposed rule of June 4, 1997 (the "Ephedra Proposal")[10] and immediately terminate this rulemaking process. In the alternative, United Metabolic requests that further attention be given to the more significant and scientifically based CANTOX Report.[11]

United Metabolic also believes that, should the FDA's proposed rule pass a court's analysis regarding the authority of the FDA, the proposed regulations still should be stricken as they would be applied to United Metabolic. In its current form, the proposed warning labels and their proposed location would, in effect, single out mail order based business, such as United Metabolic. The FDA's goal of regulation at the point of purchase in its currently proposed format would require a mail order dietary supplement provider, such as United Metabolic, to make unreasonable changes in its pamphlets and other materials that cannot be equated to the ordinary over-the-counter sale of the same supplements. Moreover, such a requirement makes little sense in light of the fact that United Metabolic's current product labeling meets, if not exceeds, the scope of the proposed rule. Thus, United Metabolic suggests an alternative location for any proposed warnings on informational materials in order to be equivalent to the point of purchase of an over-the-counter supplement.

In addition to its substantive objections to the proposed rule, United Metabolic believes that the Agency has denied the dietary supplement industry (the "Industry") a fair opportunity to review the administrative record due to the stringent time-frames granted to the Industry to submit comments to the Agency. United Metabolic believes that the regulatory process structured by the FDA denies the Industry the opportunity to fairly respond to any alleged new evidence and analyses by the Agency. In the current situation, United Metabolic has had thirty (30) days to review the material that the FDA had years to review. Moreover, the RAND Report notes that its reviewers were only given eight (8) weeks to review the available material.[12]

At a minimum, United Metabolic believes that a comment period of 180 days (with a 180 day advance notice of the termination of the comment period) should have been granted to enable the Industry to conduct a full review of the administrative record. We believe this procedural lapse, alone, renders the entire rulemaking process "arbitrary and capricious," as it fails to provide the

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[9] *Id.*, at 30.

[10] 62 Fed. Reg. 30678 (June 4, 1997).

[11] *Safety Assessment and Determination of a Tolerable Upper Limit for Ephedra*, Cantox Health Sciences International, December 19, 2000.

[12] *Supra*, note 2 at 200.

Industry with sufficient time to assert its position and apply its legal right to comprehensively review the administrative record.

I. If Finalized, a Reviewing Court Would Set Aside the Proposed Ephedrine Alkaloid Rule Because It Exceeds FDA's Statutory Authority Under the FFDCA.

The Administrative Procedures Act ("APA") requires a reviewing court to set aside agency actions, including rulemakings that are "in excess of statutory jurisdiction, authority, or limitations, or short of statutory right."[13] To assess whether an agency has overstepped its bounds, a court may begin by inquiring whether Congress intended to give an agency jurisdiction over a particular matter.[14] If the intent is clear, the court and the agency must give effect to the unambiguously expressed intent of Congress.[15]

Congressional intent is particularly important in the instant case because the FDA is attempting to expand the scope of its jurisdiction. The plain language of the FFDCA, as amended by DSHEA is clear – the FFDCA authorizes the FDA to regulate "adulterated" dietary supplements only on a product-by-product basis, not a class basis.[16] The proposed rule exceeds this authority because it attempts to regulate all dietary supplements containing ephedrine alkaloids on a class basis, rather than on a product-by-product basis.

II. FDA's Reliance on the RAND Report and AERs, Despite Widespread Condemnation by the GAO and the Agency Itself, is "Arbitrary and Capricious" in violation of the APA.

Upon the FDA's release of the Ephedra Proposal in 1997, numerous industry groups and the Small Business Administration's ("SBA") Office of Advocacy challenged the proposed rule claiming that the AERs used to support the rule were poor and unreliable.[17] Moreover, the

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[13] 5 U.S.C.A. § 706(2)(C)(2003); *Bowen v. Georgetown Univ. Hosp.*, 488 U.S. 204, 208 (1988); *Chrysler Corp. v. Brown*, 441 U.S. 281, 302 (1979)("[T]he exercise of quasi-legislative authority by governmental departments and agencies must be rooted in a grant of such power by the Congress . . . "); *Killip v. Office of Personnel Management*, 991 F.2d 1564, 1569 (Fed. Cir. 1993)("Any and all authority pursuant to which an agency may act ultimately must be grounded in an express grant from Congress").

[14] *Chevron U.S.A., Inc. v. Natural Resources Defense Council, Inc.*, 467 U.S. 837, 842-43 (1984); *Mova Pharmaceutical Corp. v. Shalala*, 140 F.3d 1060, 1067-68 (D.C. Cir. 1998).

[15] *Chevron*, 467 U.S. at 842-43; *See also Adams Fruit Co. v. Barrett*, 494 U.S. 638, 649 (1990)("[A] precondition to deference under *Chevron* [to an agency interpretation] is a congressional delegation of administrative authority").

[16] Pub. L. 103-417; 21 U.S.C.A. §§ 342(f)(1)(2003); *See also FDA Statement on Street Drugs Containing Botanical Ephedrine*, FDA Press Release, April 10, 1996 (stating that "under recent amendments to [the FFDCA], the agency has to act [on dietary supplements] 'product-by-product' and the legal burden is now on the FDA to show that a marketed [dietary supplement] product is unsafe, rather than on the company to gain FDA approval by showing that the product was safe before it is marketed").

[17] Letter dated February 3, 1998 from the SBA to the FDA regarding the Ephedra Proposal.

Agency[18] and Congress[19] agreed that AERs contained numerous limitations. Finally, the United States General Accounting Office concluded that AERs suffered from numerous "inherent weaknesses" that "lead to uncertainty" in the proposed rule.[20] In the face of this widespread condemnation of the use of AERs, the FDA withdrew the proposed requirements concerning potency, labeling claims, and directions for use, but not the proposed warning statement or the proposed prohibition on dietary supplements that combine ephedrine alkaloids with other stimulant ingredients, such as caffeine.[21] Nothing has changed since that time regarding the unreliability of AERs.[22]

Nevertheless, as the following comments clearly indicate, the FDA has again relied upon AERs in order to support its proposed rulemaking.

A. The GAO report

In July of 1999, the United States General Accounting Office ("GAO") published a report entitled "Uncertainties in Analyses Underlying FDA's Proposed Rule on Ephedrine Alkaloids" (the "GAO Report"). The GAO published its report after Congress asked it to address the scientific basis for the FDA's proposed rule, specifically, with respect to the use of AERs. In preparing the GAO Report, the GAO performed a content analysis of the AERs and reviewed the scientific literature and case reports of adverse events from products containing ephedrine alkaloids.[23] The GAO Report ultimately concluded that the substantive aspects of the FDA's proposed rule that Congress asked it to review (dosage level and frequency restrictions) were "open to question" due to limitations and uncertainties in the Agency's scientific and economic analyses.[24]

According to the GAO Report, the AERs relied upon by the FDA were "poorly documented"[25] and inconsistent because the AERs are a "passive surveillance system" that rely on consumers

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[18] *See* Statement of Joseph A. Levitt, *How Accurate is the FDA's Monitoring of Supplements Like Ephedra?*, House Committee on Government Reform Hearing, May 27, 1999, at 17-19.

[19] *See* Opening Statement, Chairman Dan Burton, *How Accurate is the FDA's Monitoring of Supplements Like Ephedra?*, House Committee on Government Reform Hearing, May 27, 1999, at 7-10.

[20] *Supra*, note 4, at 10.

[21] 68 FR 10417, 10418 (March 5, 2003).

[22] In fact, the GAO recently restated its position that AERs are inherently unreliable. GAO Report, *Dietary Supplements for Weight Loss: Limited Federal Oversight has Focused More on Marketing than on Safety*, July 31, 2002 at 4 (stating that "there are numerous problems with this passive system of adverse event reporting, and these have been noted extensively in our earlier work).

[23] *Supra*, note 4 at 2.

[24] *Id.* at 3.

[25] *Id.* at 8.

and their friends and family members, along with physicians, health care professionals, product manufacturers and state health agencies to "voluntarily report adverse events."[26] In addition, the GAO Report found that the FDA:

> used AERs as the sole source of support for specific dosing levels, relied on weak information to set limits on duration of use, and did not perform a causal analysis to determine whether ingestion of a dietary supplement containing ephedrine alkaloids caused or contributed to the adverse events.[27]

The GAO Report ultimately concluded that AERs have the following limitations: different interpretations in determining an adverse event; inaccurate reporting of adverse events; biases in spontaneous reporting systems; estimation of population exposure; and report quality.[28] Moreover, the GAO Report determined that with regard to differing interpretations, AERs are "subjective and imprecise."[29] Based on these weaknesses of AERs, the GAO Report recommended that the FDA obtain additional information, other than AERs, before proceeding to any final rulemaking.[30]

B. The SBA, Congress, and the FDA Believe that AERs are Inherently Flawed.

In addition to the GAO, the SBA also has criticized the FDA's use of AERs to support the Ephedra Proposal.[31] In its February 3, 1998 comments to the FDA, the SBA noted that by the FDA's own admission, AER's are not reliable sources of data.[32] According to the SBA:

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[26] *Id.* at 5.

[27] *Id.* at 8.

[28] *Id.* at 35.

[29] *Id.*

[30] *Id.* at 3. In addition, the GAO has reiterated its position regarding the weaknesses of AERs as recently as July of 2002. GAO Report, *Dietary Supplements for Weight Loss: Limited Federal Oversight has Focused More on Marketing than on Safety*, July 31, 2002 at 4 (stating that "there are numerous problems with this passive system of adverse event reporting, and these have been noted extensively in our earlier work").

[31] *Supra*, note 17.

[32] *Id.* at 3. According to the SBA, the FDA acknowledged in the Ephedra Proposal that:

> [a] possible source of serious error in evaluating observational data, such as that found in FDA's postmarketing surveillance system, is the potential for inappropriately assuming that a cause and effect relationship exists between a particular exposure and a particular adverse event without evaluating the true relationship of the adverse event to the exposure . . . many of the AERs did not provide enough information to adequately evaluate . . . [causality].

Id. (quoting 62 Fed. Reg. 30,689-90).

> AERs are "inherently inconclusive and lacking in vital data, and no reasonable person could draw any conclusion regarding causality from the information provided – especially the conclusion that ephedrine alkaloids were the cause of the reported illness.[33]

Thus, the SBA concluded that "the faulty data, inappropriate data assumptions, and other serious errors all contributed to the faulty analysis – an analysis that overestimates the benefits and undermines the entire rulemaking [process]."[34]

Congress has echoed the concerns of the SBA regarding the inherent flaws with the FDA's use of AERs. On May 27, 1999, the House Committee on Government Reform held a hearing regarding the accuracy of the FDA's monitoring of dietary supplements, including ephedra.[35] During this hearing, the committee recognized that the FDA's system of AERs contains "shortcomings" that affect the accuracy of the system.[36] In fact, the committee identified the following problem areas in the current system of AERs:

- **A causal relationship is not established.** The FDA does not conduct any analysis of possible causal relationships between products and adverse reactions for dietary supplements. Moreover, the FDA does not follow-up to make sure that an adverse event is actually caused by a dietary supplement.[37]

- **The seriousness of an event is not classified.** The FDA does not evaluate whether the adverse events are mild events, moderate events or serious events, which gives the impression that "all of these events are serious events."[38]

- **Identification of brand and corporate names without confirmation.** The FDA allows the publishing of the brand and corporate names for the product without determining whether the product actually caused the event or whether the patient actually consumed the product.

- **The FDA does not purge incorrect information from its AERs.**[39]

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[33] *Supra*, note 17, at 4.

[34] *Id.* at 5.

[35] *How Accurate is the FDA's Monitoring of Supplements Like Ephedra?*, House Committee on Government Reform Hearing, May 27, 1999.

[36] Opening Statement, Chairman Dan Burton, *How Accurate is the FDA's Monitoring of Supplements Like Ephedra?*, House Committee on Government Reform Hearing, May 27, 1999, at 7-10.

[37] *Id.* at 7.

[38] *Id.* at 8.

[39] *Id.* at 10.

Based on these problems, the committee determined that the FDA's use of AERs amounted to an "ineffective system" that needed to be remedied.[40]

Finally, the FDA itself has realized that AERs contain numerous limitations to their usefulness.[41] During this same hearing, the Director of the FDA's Center for Food Safety and Applied Nutrition ("CFSAN") testified that:

> [t]he major limitations to consider when assessing spontaneously reported information is underreporting of adverse events, report quality, adverse event recognition or attribution, reporting biases that are inherent and estimation of population exposure.[42]

Furthermore, due to the express limitations of AERs, in prior rulemakings, the FDA has relied on AERs only in conjunction with other more reliable clinical studies.[43] Nevertheless, despite the numerous limitations of the AERs recognized by both Congress and the FDA, and despite the GAO's recommendations, the FDA is once again attempting to regulate the Industry based on the Adverse Event Reports.

C. The FDA's Continued Reliance on AERs through the RAND Report.

The FDA's use of the RAND Report as the backbone of yet another attempt to regulate dietary supplements containing ephedra or ephedrine requires the FDA to base its rulemaking on AERs. Moreover, the comments by the Industry, the SBA, the GAO, Congress and the FDA regarding the unreliability of AERs remain applicable to the present situation.

To their credit, unlike the FDA's current proposed regulations, the authors of the RAND Report at least attempted to look outside the AERs in order to assess the safety of dietary supplements. Specifically, the RAND Report first examined 52 clinical trials of ephedrine and herbal ephedra for weight loss or athletic performance in humans. According to the RAND Report, the "strongest evidence for causality should come from clinical trials."[44] However, the RAND Report clearly found "no serious adverse events (e.g. death, myocardial infarction, stroke, etc.)

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[40] *Id.* at 11.

[41] *See* Statement of Joseph A. Levitt, *How Accurate is the FDA's Monitoring of Supplements Like Ephedra?*, House Committee on Government Reform, May 27, 1999, at 19.

[42] *Id.*

[43] *See, e.g.,* 44 Fed. Reg. 7212 (June 26, 1979)(relying upon AERs in addition to other studies in determining whether to regulate Yellow No. 5); 49 Fed. Reg. 13679 (April 6, 1984)(scaling back a proposed warning label after a federal district court held that the severity of the original warning was not substantially supported by the administrative record, which consisted mostly of AERs).

[44] *Supra*, note 2 at xvi.

were reported in the 52 clinical trials."[45] Moreover, given the small numbers of persons actually studied in the clinical trials, even in the aggregate, the trials only had sufficient statistical power to detect a serious adverse event rate of 1.0 in 1000.[46] Generally, the conventional definition of a "rare" adverse event is approximately one in 1000.[47] Consequently, the RAND Report fell back on the FDA's faithful adherence to AERs, despite the concerns brought forth by the GAO Report.

The RAND Report examined approximately 17,000 AERs that were provided to it by both the FDA and by Metabolife, a manufacturer of Ephedra-containing supplements products. However, despite the volume of AERs reviewed, the authors of the RAND Report could neither assess nor determine a causal relationship between the use of ephedra-containing dietary supplements and any serious adverse events.[48] According to the RAND Report:

> 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.[49]

In addition, the RAND Report recognized several other "major" limitations on its conclusions due to the use of AERs, including the following:

- The majority of case reports were insufficiently documented;[50]
- The number of events were underestimated because patients need to suspect an association in order to report an event;[51]
- The reliance on AERs only effectively excluded review of other lines of evidence, such as animal studies, basic neuroscience studies, and adverse event data concerning other sympathomimetic amines that some authorities consider important when trying to assess causation;[52]

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[45] *Id.* at 79. (Emphasis added).

[46] *Id.*

[47] *Id.*

[48] *Id.* at 199.

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

[50] *Id.* at xvi.

[51] *Id.* at 199.

[52] *Id.*

- The AERs were poorly documented and contained insufficient evidence such that many of the AERs did not contain all the data that was needed to make assessments;[53]

- Most of the evidence reviewed as to the Metabolife files was handwritten, suggesting that the reviewers may not have correctly interpreted the writer's intentions;[54]

- The Metabolife files were not recorded in an organized fashion and were subject to various interpretations;[55]

- The evidence suggested recording bias because each of the files reviewed did not contain the same information; [56] and

- The likelihood of double counting of adverse events exists because the authors could not identify all of the files associated with a single case.[57]

In its conclusion, related to the need for future research, the RAND Report effectively summed up the inherent flaws with relying solely on AERs:

> In order to assess a causal relationship between ephedra and ephedrine consumption and serious adverse events, a hypothesis-testing study is needed. Continued analysis of case reports cannot substitute for a properly designed study to assess causality. A case-control study would probably be the study design of choice.[58]

In other words, the authors of the RAND Report could not determine that a "significant or unreasonable risk of illness or injury" exists solely from the AERs. As stated previously, the FDA's burden of proof under DSHEA requires such a finding. Therefore, it is beyond the realm of reason for the FDA to continue to claim that AERs provide sufficient support for its proposed regulations and warning labels when the FDA's own "hired gun" (the RAND Corporation) could not draw such a conclusion.

D. FDA's Reliance upon AERs in this Rulemaking is "Arbitrary and Capricious in Violation of the APA.

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[53] *Id.*

[54] *Id.*

[55] *Id.*

[56] *Id.*

[57] *Id.* at 199.

[58] *Id.* at xvii; *Id.* at 205. (Emphasis added).

Based on the foregoing, it is clear that the FDA's proposed rulemaking would be "arbitrary and capricious" in violation of the APA. It is well established that, pursuant to the APA, courts may set aside an agency regulation if it is "arbitrary and capricious" or substantially unsupported by the factual record.[59] Although a reviewing court may not substitute its judgment for that of the agency under this standard, the court may intervene to ensure that the agency "examine[d] the relevant data and articulate[d] a satisfactory explanation for its action."[60] Further, a reviewing court may undo an agency's action if the agency failed to provide a reasoned explanation for its action, or if the administrative record belies the agency's conclusion.[61] According to the United States Supreme Court, the test to be applied is "whether a reasonable mind might accept a particular evidentiary record as adequate to support a conclusion."[62] Under this standard, the administrative record for the FDA's proposed rule, including the RAND Report, fails to support the proposal to regulate, in any manner, dietary supplements containing ephedrine alkaloids.

The administrative record in the instant case includes the RAND Report that relied on approximately 17,000 AERs. However, these AERs suffer from the same deficiencies noted by the GAO Report (i.e. that AERs are inherently unreliable). Based on the GAO Report and the Industry comments, the FDA should not rely on the faulty data of AERs to support the prohibition of ephedrine alkaloids or any new restrictions on the use thereof. To be sure, should the FDA continue such use of AERs, a reviewing court would set aside the ephedrine alkaloid rulemaking under the "arbitrary and capricious" standard. Without the use of these unreliable AERs, the FDA has no basis for any action.

In fact, under the "arbitrary and capricious" standard, courts frequently find that any regulation or agency decision not adequately supported by evidence and without scientific data in the administrative record must be set aside. In the following cases, courts have set aside rulemakings as "arbitrary and capricious" when the scientific evidence had the following deficiencies:

- The Occupational Safety and Health Administration's ("OSHA") administrative record for a rule did not contain evidence that: (1) definitively proved that benzene was dangerous above the proposed exposure limit; (2) demonstrated a dose-response relationship to support the proposed limit; and

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[59] 5 U.S.C.A. § 706(2)(2003); (Emphasis added). *Dickinson v. Zurko*, 527 U.S. 150, 164 (1999)(absent an exception, a court will not uphold factual findings made by any agency if the findings are "arbitrary and capricious" or insufficiently "bound up with a record-based factual conclusion"); *Motor Vehicles Manufacturers Ass'n of the United States v. State Farm Mutual Auto. Ins. Co.*, 463 U.S. 29, 43 (1983)(reviewing the rescission of an informal rule pursuant to Section 706(2)(A) of the APA and articulating the "arbitrary and capricious" standard of review.

[60] *State Farm*, 463 U.S. at 43 (quoting *Burlington Truck Lines v. United States*, 371 U.S. 156, 168 (1962)); *See County of Los Angeles v. Shalala*, 192 F.3d 1005, 1021 (D.C. Cir. 1999)(quoting *State Farm* and holding that a determination made by the Secretary of the Department of Health and Human Services ("HHS") was "arbitrary and capricious" because her conclusions belied the underlying data).

[61] *County of Los Angeles*, 192 F.3d at 1021.

[62] *Zurko*, 527 U.S. at 162 (citations omitted).

(3) supported its assumption that the risk of adverse events would decrease as exposure to benzene decreased.[63]

- The FDA's administrative record for a rule contained a scientifically flawed survey, upon which FDA relied to promulgate the regulation at issue.[64]

- The Department of Health and Human Services' ("HHS") administrative record for a rule contained statistics that had been compiled for a limited purpose, and HHS relied upon those statistics to promulgate the rule at issue, even though the statistics did not apply to the rule at issue.[65]

The foregoing examples directly apply to the FDA's proposed rule regarding dietary supplements containing ephedrine alkaloids because, in the instant case, the "scientific evidence" relied upon by the Agency is even weaker than the evidence relied upon in the above cases. Here, the FDA has relied almost exclusively on the RAND Report that relied on discredited AERs to provide the "scientific support." Based on the above, such weak evidence would be insufficient to support any restrictive rulemaking and would be set aside as "arbitrary and capricious."

In addition, some courts have found an agency action to be "arbitrary and capricious" or have condemned the agency action, where the agency ignored reliable third-party reports and criticisms.[66] In the instant case, there is little doubt that a court would find the FDA's attempt to ignore the concerns of the GAO, an unbiased third-party, as well as similar concerns expressed by Congress, the SBA, the Industry, and the Agency, itself, to be particularly egregious. FDA's continued reliance upon the faulty data of AERs demonstrates an unwillingness to veer off its

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[63] *Industrial Union Dept. v. American Petroleum Inst.*, 448 U.S. 607 (1980).

[64] *Almay v. Califano*, 569 F.2d 674, 682-83 (D.C. Cir. 1978).

[65] *De Soto General Hospital v. Heckler*, 766 F.2d 182, 183-85 (5th Cir. 1985); *See also St. James Hospital v. Heckler*, 760 F.2d 1460, 1468 (7th Cir. 1985)(holding same rule was "arbitrary and capricious"); *Humana of Aurora, Inc. v. Heckler*, 753 F.2d 1579, 1583 (10th Cir. 1985)(same); *Lloyd Nolan Hospital v. Heckler*, 762 F.2d 1561, 1568 (11th Cir. 1985)(same); *Abington Memorial Hospital v. Heckler*, 750 F.2d 242, 243 (3d Cir. 1984)(same); *Walter O. Boswell Memorial Hospital v. Heckler*, 749 F.2d 788, 803 (D.C. Cir. 1984)(remanding a district court decision, which upheld the rule, and signaling that the agency's reliance on inadequate empirical information rendered the regulation "arbitrary and capricious").

[66] *See, e.g., A.L. Pharma, Inc. v. Shalala*, 62 F.3d 1484, 1492 (D.C. Cir.1995)(FDA's promulgation of a final rule was "arbitrary and capricious" because the FDA failed to respond to criticisms from the scientific community); *National Parks and Conservation Ass'n v. Federal Aviation Administration ("FAA")*, 998 F.2d 1523, 1533 (10th Cir. 1993)(FAA's disregard of a National Park Service report that contradicted the FAA's conclusion that a new airport would have no significant impact on the environment was "arbitrary and capricious"); *Hillsman v. Bowen*, 804 F.2d 1179, 1181-82 (11th Cir. 1986)(administrative law judge's denial of a claimant's petition for social security disability benefits was "arbitrary and capricious" because it ignored a contradictory report submitted by the treating physician); *Sierra Club v. United States Army Corps of Engineer ("COE")*, 701 F.2d 1011, 1032-33 (2d Cir. 1983)(COE's approval of an Environmental Impact Statement and issuance of a dredge and fill permit was "arbitrary and capricious" because the agency failed to address criticisms from several other agencies and failed to consider a contradictory biological study contained in the administrative record); *Cobell v. Babbit*, 91 F.Supp. 2d 1, 52-53 (D.D.C. 1999).

predetermined course of action, irrespective of directly contradictory evidence. Accordingly, a reviewing court would set aside the FDA's final rulemaking as "arbitrary and capricious."

III. FDA's Proposed Regulations and Prohibitions on Ephedrine Alkaloids are Arbitrary and Capricious Because There is a Lack of Scientific Evidence to Support a Health or Safety Concern.

Even assuming that a reviewing court would determine that the FDA's authority has not been exceeded in instituting its proposed regulations, a court would nonetheless still find the regulations to be "arbitrary and capricious" due to the lack of a scientific basis to support such regulations. In fact, most studies have concluded that dietary supplements containing ephedrine alkaloids are safe and effective when used under recommended dosages.[67]

The absence of a safety concern associated with dietary supplements that contain ephedrine alkaloids is demonstrated by clinical and pre-clinical studies, the lack of documented and verified adverse events associated with the products, and the report of Cantox Health Sciences International ("CANTOX"), at the request of the Council for Responsible Nutrition (the "CANTOX Report").[68] Together, this information illustrates that approximately 2 to 3 billion doses of dietary supplements containing ephedrine alkaloids are consumed annually.[69] Moreover, it is estimated that over half of the citizens in the United States use some form of dietary supplements and spend approximately 14 billion dollars annually on such products.[70] However, despite the volume of usage, the CANTOX Report found only 1,173 AERs reported to the FDA in connection with the use of dietary supplements containing ephedrine alkaloids.[71] As the CANTOX Report stated:

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[67] *See Safety Assessment and Determination of a Tolerable Upper Limit for Ephedra*, Cantox Health Sciences International, December 19, 2000; *See also See* Greenway, F.L., *The safety and efficacy of pharmaceutical and herbal caffeine and ephedrine use as a weight loss agent*, International Association for the Study of Obesity, Obesity Reviews, (2001) 2: 1999-211 (concluding that the weight loss benefits of these products "appear to outweigh the small associated risks); Kimmel, S., *Background risk of seizures, strokes, and myocardial infarction compared to the incidence of such events in persons consuming dietary supplements containing ephedrine alkaloids*, (2000)(concluding that "the use of dietary supplements containing ephedrine alkaloids does not increase the risk of seizures, strokes or heart attacks") (Emphasis added); de Jonge, L., *Safety and efficacy of an herbal dietary supplement containing caffeine and ephedra for obesity treatment*, Pennington Biomedical Research Center, Louisiana State University, October 2001; and Morgenstern, L.B., et al., *Use of Ephedra-containing products and risk for hemorrhagic stroke*, Neurology 2003; 60:132-135 (concluding that Ephedra is not associated with increased risk for hemorrhagic stroke, except possibly at higher doses). (Emphasis added).

[68] *Supra*, note 11.

[69] *Id.* at 65 (citing the GAO Report, *supra*, note 4).

[70] *Supra*, note 11, at 1, 64-65.

[71] *Id.* at 65.

> [a] total of 1,173 AERs for over 2 to 3 billion doses indicates that there is good margin of safety for dietary supplements containing ephedrine alkaloids in the general healthy population.[72]

The above data compares favorably with virtually any food or dietary supplement product sold in the United States.[73] Such overwhelming data does not evidence a safety problem associated with dietary supplements that contain ephedrine alkaloids.

As described more fully herein, the FDA's regulations are based upon the findings in the RAND Report where approximately 17,000 AERs plus clinical trials were reviewed.[74] However, contrary to the FDA's assertions, the RAND Report does not establish any causal relationship between the use of dietary supplements containing ephedrine or ephedra and serious adverse events.[75] Consequently, based upon the RAND Report, the FDA cannot satisfy its burden under DSHEA to establish that there exists a "significant or unreasonable risk of illness under conditions of use recommended or suggested in labeling."[76] Thus, the FDA's proposed regulations would be held by a court to be "arbitrary and capricious" in violation of the APA due to the lack of scientific evidence to support such regulations. Moreover, the FDA could not institute a prohibition on the use of dietary supplements containing ephedrine alkaloids.

A. The RAND Report

The National Institutes of Health ("NIH") Office of Dietary Supplements ("ODS") commissioned the RAND Corporation to assess the safety and efficacy of herbal ephedra-containing dietary supplements.[77] In connection therewith, the ODS posited the following seven questions for the RAND Report to address:

> (1) Does use of ephedra-containing dietary supplement products over a sustained period of time increase the risk of cardiovascular disease (CVD) or other serious and life-threatening events in specific populations?
> (2) What populations are at risk of CVD and other life-threatening events through use of ephedra over a sustained period of time?
> (3) Can the risk of adverse events in these populations be attributed to ephedra alone, or in combination with other ingredients (e.g. caffeine)?

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[72] *Id.* at 65.

[73] Many foods, such as peanuts, strawberries, fish, eggs, dairy products, soy products and wheat are subject to significantly more adverse reactions than dietary supplements containing ephedrine alkaloids, including seizures and occasionally death.

[74] 68 Fed. Reg. 10417, 10418 (March 5, 2003).

[75] *Supra*, note 2 at vi, xvi, 30-32, 199, 203.

[76] 21 U.S.C.A. § 321(f)(1)(A).

[77] *Supra*, note 2 at v.

(4) Does ephedra have additive effects with other agents?
(5) What dosage levels of ephedra produce risk of CVD or other life-threatening events?
(6) Do ephedra-containing dietary supplement products alter physiologic markers of cardiovascular function?
(7) What are the metabolic actions of ephedra, so as to explain its beneficial and adverse effects?

In order to assess the safety of the dietary supplements containing herbal ephedra, the RAND Report reviewed 52 clinical trials and approximately 17,000 AERs, provided by the FDA and Metabolife.[78] However, despite the volume of information reviewed, the RAND Report conceded that it could not establish a relationship between the dosage and the likelihood of serious adverse events. According to the RAND Report:

> One of the key questions we were asked to answer by the sponsoring agencies concerned the relationship between dose and the likelihood of serious adverse events. We do not believe such an analysis is justifiable based on the case report evidence presented here, for the following reasons. First, such an analysis assumes a cause-and-effect relationship that has not been proven by conventional standards of medical science. Second, it would rely to a great extent on patients' recall of dose after having suffered an adverse event, which increases the likelihood of recall bias. Third, and most important, for more than half the adverse-event cases, no dose data were available.[79]

Despite the failure of the RAND Report to establish any causal relationships between the use of ephedra-containing dietary supplements and any serious adverse events, the RAND Report did reach one important conclusion. According to the RAND Report, there **is** an association between the short-term use of ephedrine, ephedrine plus caffeine, or dietary supplements that contain ephedra with or without herbs containing caffeine and a statistically significant increase in short-term weight loss (compared to placebo).[80]

With respect to the 52 clinical trials, the findings of the RAND Report clearly did not establish a "significant or unreasonable risk of illness." The RAND Report reviewed every clinical trial for any data related to adverse events, regardless of the treatment duration, and then compared the event rates for ephedra and ephedrine to those in the placebo groups.[81] According to the RAND Report, placebo-controlled randomized clinical trials would produce "the strongest level of evidence for attributing an adverse event to an exposure."[82]

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[78] *Id.*, note 2 at xiv.

[79] *Id.* at 32. (Emphasis added).

[80] *Id.*, at xvi. (Emphasis added).

[81] *Id.* at xv. (Emphasis added).

[82] *Id.* at 24.

However, the RAND Report concluded that the clinical trials were simply insufficient to assess the adverse event rate for the use of ephedra-containing dietary supplements.[83] After reviewing all adverse events reported from the 52 clinical trials regarding ephedra and ephedrine, the RAND Report found no serious adverse events (e.g. death, myocardial infarction, stroke, seizures and severe psychiatric symptoms).[84] This is particularly important in that the reviewers acknowledged that they may have overestimated the number of adverse events.[85] Moreover, the reviewers concluded that due to the small number of patients studied in the trials, even in the aggregate, the clinical trials only had statistical power to detect an adverse event rate of one out of 1000.[86] As the RAND Report recognized, the conventional definition of a "rare" adverse event is approximately one out of 1000.[87] The authors of the RAND Report did find an association between the use of ephedrine and/or the use of ephedra-containing herbal and an increased risk of nausea, vomiting, anxiety, mood changes, hyperactivity and palpitations.[88] Nevertheless, based on the results of their review of clinical studies, the RAND Report primarily focused on the reviewers' assessment of AERs regarding serious events allegedly associated with the use of ephedra.[89]

With respect to the RAND Report's primary focus (i.e. the review of over 17,000 AERs), the authors did not fare much better than the clinical studies. The RAND Report acknowledged that AERs lacked sufficient documentation to make an informed judgment regarding any relationship between the use of ephedrine or ephedra-containing dietary supplements and serious adverse events.[90] Moreover, due to the subjectivity involved with assigning causality to AERS, the RAND Report simply avoided even attempting an assessment of causation:

> Many of the peer review comments received for this report pertained to our attempts to assign causality. These comments varied widely, ranging from critiques of our method for being too conservative (meaning, in the opinion of some reviewers, we had excluded or assigned too low a level of causality to certain cases) to critiques for being too liberal (meaning, in the opinion of some reviewers, we had assigned too high a level of causality to certain cases). Often,

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[83] *Id.* at 79.

[84] *Id.* at 79, 203. (Emphasis added).

[85] *Id.* at 24.

[86] *Id.* at 79, 203.

[87] *Id.* at 79. (Emphasis added).

[88] *Id.* at vi.

[89] *Id.* at 26, 80.

[90] *Id.* at vi.

> these conflicting comments concerned the same cases. We believe that these peer review comments demonstrate that case report reviews involve considerably more subjective interpretation than do reviews of randomized trials. Because our goal in this evidence report is to report the evidence as objectively as possible, we ceased to assign assessments of causality to the case reports.[91]

In lieu thereof, the RAND Report assigned the AERs to classifications based on the potential role of ephedra or ephedrine in causing an adverse event.[92] Serious adverse events (such as death, myocardial infarction, seizures, stroke and severe psychiatric symptoms) were assigned as either "sentinel events," "potential sentinel" events or as having "insufficient information" in which to classify the event.[93] Although the intent may have been to show some relationship, the RAND Report repeatedly emphasized that "classification as a sentinel event does not imply a cause and effect relationship."[94]

After reviewing approximately 17,000 AERs, the RAND Report could only identify a total of thirty-three (33) cases as "sentinel events" and only fifty (50) cases as "potential sentinel events."[95] Furthermore, upon a closer inspection of the AERs, the relationship between the adverse event and the use of ephedra or ephedrine is even weaker than claimed by the RAND Report. In fact, most of the subjects identified in the AERs by the RAND Report actually had pre-existing health conditions or had been taking the ephedrine/ephedra in dosages exceeding the recommended amounts. For example, with respect to the seventeen (17) death cases classified as "sentinel" or "potential sentinel" events, the following additional information should be considered:

Preexisting health conditions where noted:
AER # 14390 - asthma and congenital hydrocephalus with a shunt placed;
AER # 9508 - bulimia, anorexia and acute myocarditis;
AER # 10276 - myocarditis, bronchiolitis, pneumonia;
AER # 12485 - triple vessel coronary artery disease and cardiomegaly;
AER # 12843 - Bland-White-Garland Syndrome;
AER # 13906 - aortic dissection;
AER # 14638 - atherosclerotic coronary vascular disease; and
AER # 224 - coronary artery disease.

Dosages in excess of recommended level (100 mg/day) where noted:
AER # 348 - 600 mg/day;

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[91] *Id.* at 30. (Emphasis added).

[92] *Id.* at 30

[93] *Id.* at 30-31.

[94] *Id.* at vi, 81, 203. (Emphasis added).

[95] *Id.* at 81, 203. (Emphasis added).

AER # 3275432;
AER # 3289590; and
AER # 44 - street drug of at least 306 mg.

The foregoing also applies with regard to the other categories of serious adverse events identified by the RAND Report. The following additional information should be considered as applied to the eleven (11) "sentinel" or "potential events" in the myocardial infarction and acute coronary syndromes category:

Preexisting health conditions where noted:
AER # 10024 - smoking and alcoholism;
AER # 9504 – hypertension;
AER # 10009 - coronary artery disease;
AER # 13009 - coronary heart disease;
AER # 14114 - coronary artery disease, overweight and cigarette smoking; and
AER # 14530 - lipid disorder, coronary artery disease and cigarette smoking.

Dosages in excess of recommended level (100 mg/day) where noted:
AER # 9372.

In regard to the twenty-three (23) "sentinel" and "potential sentinel" events in the cerebrovascular accident / stroke category, the following additional information should be considered:

Preexisting health conditions where noted:
AER # 10874 - IV drug abuse, alcoholism, and cigarette smoking;
AER # 11105 - cigarette smoking;
AER # 11675 - cigarette smoking;
AER # 552 - cigarette smoking;
AER # 184 - alcoholism, anorexia and bulimia;
AER # 9335 - hypertension and cigarette smoking;
AER # 10094 - antiphospholipid antibody syndrome;
AER # 12713 - hypertension, paroxysmal atrial fibrillation and history of transient ischemic attacks;
AER # 12733 – hypertension;
AER # 12888 - vasculitis;
AER # 4434 - hypertension and hypercholesterolemia; and
AER # 14553 - aneurysm.

Dosages in excess of recommended level (100 mg/day) where noted:
AER # 11105 - consumed approximately six pills at a time;
AER # 184 - possible suicide by taking 15 – 18 pills at one time;
AER # 9296;
AER # 9335;
AER # 44; and

AER # 438.

In regard to the three (3) "potential sentinel" events in the cardiovascular category, the following additional information should be considered:

Preexisting health conditions where noted:
AER # 297 – hypertension.

Dosages in excess of recommended level (100 mg/day) where noted:
AER # 110 - 2000 mg/day.

In regard to one (1) "potential sentinel" event in the other neurological category, the following additional information should be considered:

Preexisting health conditions where noted:
AER # 13062 - hyperthyroidism, reflux disease, depression, degenerative joint disease and fibromyalgia.

In regard to the nine (9) "sentinel" and "potential sentinel" events in the seizure category, the following additional information should be considered:

Preexisting health conditions where noted:
AER # 9534
AER # 10432 - alcoholism, diabetes, and organic brain syndrome;
AER # 11649 - underlying seizure disorder;
AER # 14571 - drug abuse and depression.

Finally, with respect to the sixteen (16) "sentinel" and "potential sentinel" events in the psychiatric category, the following information should be considered:

Dosages in excess of recommended level (100 mg/day) where noted:
AER # 1855921 - 40 tablets per day;
AER # 238;
AER # 285 - 360 mg/day; and
AER # 1661966 - 1250 mg/day.

The foregoing additional information tends to indicate that there may not be any connection between the AERs and the use of ephedra or ephedrine. Despite such a possibility, however, the RAND Report determined that these AERs should be labeled as "sentinel" or "possible sentinel" events without any definitive evidence to suggest a relationship with the use of ephedra or ephedrine. When these faulty conclusions are coupled with the inherent unreliability of AERs (as discussed previously), the credibility of the RAND Report's conclusions based on AERs must be drawn into question due to the lack of scientific evidence.

In the end, the RAND Report acknowledged its inability to establish a causal connection between the use of ephedra-containing dietary supplements and serious adverse events.[96] In fact, the best the RAND Report could offer to the FDA was a recommendation for further research to establish such a causal relationship.[97] Based on these findings, it is effectively impossible for the FDA to have established a "significant or unreasonable risk of illness or injury," as required by DSHEA. Accordingly, any attempt by the FDA to prohibit dietary supplements containing ephedra and/or ephedrine would be struck down by a court as "arbitrary and capricious" in violation of the APA. Moreover, any other proposed regulations would suffer the same fate at the hands of a reviewing court.

With respect to the RAND Report's future research section, the authors recommended a controlled clinical study to assess "the possible association of ephedra or ephedrine consumption and the occurrence of serious adverse events.[98] United Metabolic agrees with the recommendation that a controlled scientific case study (not additional AERs) is necessary in order to assess any possible association between the consumption of ephedra-containing dietary supplements and serious adverse events.[99] Likewise, United Metabolic agrees that further attention needs to be given to the results of numerous studies that have taken place in Denmark, where doctors have prescribed an ephedrine-containing diet drug for more than 20 years.[100] These studies have consistently found that the ephedrine and caffeine combination is "safe and effective" and any side effects from the use thereof, are "minor and transient."[101]

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[96] *Supra*, note 2 at 202.

[97] *Id.* at vii.

[98] *Id.* at 205

[99] *Id.* at 203, 205. In addition to the RAND Report, the *Boozer* study recommended a randomized, placebo controlled trial to evaluate cause and effect relationships versus coincidental events in the use of ephedra / ephedrine alkaloids. *See* Boozer, C.N., *Herbal ephedra / caffeine for weight loss: a 6-month randomized safety and efficacy trial*, International Journal of Obesity (2002) 26, at 602. According to the *Boozer* study, it is "impossible from adverse event reports alone" to determine whether adverse events occur at a higher rate in a population currently undergoing treatment than in an untreated group. *Id.* (Emphasis added). As stated previously, United Metabolic likewise supports such an effort and will assume the lead in the study should the FDA agree with that course of action.

[100] *Supra*, note 2, at 205.

[101] *See* S. Toubro, et al, *The acute and chronic effects of ephedrine / caffeine mixtures on energy expenditure and glucose metabolism in humans*, 17 International Journal of Obesity and Related Metabolic Disorders (Supplement 3) S73, S82 (1993); *see also* L. Breum, et al., *Comparison of ephedrine / caffeine combination and dexfenfluramine in the treatment of obesity: a double-blind multi-centre trial in general practice*, 18 International Journal of Obesity and Related Metabolic Disorders 99 (1994); A. Astrup, et al., *The effect and safety of an ephedrine/caffeine compound compared to ephedrine, caffeine and placebo in obese subjects on a restricted diet*, 16(4) International Journal of Obesity and Related Metabolic Disorders 269 (1992); A Malchow-Miller, *Ephedrine as an anoretic: the story of the Elisnore Pill*, 5(2) International Journal of Obesity and Related Metabolic Disorders 183 (1981)(involving a placebo controlled study with 132 clinically obese people on a 1200 calorie/ day diet taking a combination of caffeine/ephedrine and concluding that "no serious side effects were observed").

B. The CANTOX Report

Due to the numerous faults with the RAND Report, United Metabolic suggests that the FDA give more detailed attention to the findings of the CANTOX Report.[102] This report prepared for the Council for Responsible Nutrition remains the only formal risk assessment that has been done to date which based its findings on non-clinical studies, clinical studies, animal data, published case reports and AERs.[103] The CANTOX Report's objectives included the establishing of a safe upper intake level for dietary supplements containing ephedrine based on the National Academy of Sciences Upper Limit Model for nutrients ("UL").[104] The UL provides a safety standard for dietary supplements containing ephedrine such that no significant or unreasonable risk of illness or injury would arise at or below this intake level.[105]

Most importantly, in reaching its conclusion, the CANTOX Report, unlike the RAND Report, discounted the significance of AERs. According to the CANTOX Report, an assessment of the AERs revealed that 98% of the AERs did not contain complete critical information.[106] However, the minimal information that could be retrieved from the AERs revealed a high standard of safety for dietary supplements containing ephedrine alkaloids in the general healthy population, when taken as recommended.[107] The CANTOX Report concluded:

> [t]he non-life threatening adverse effects that were reported were attributable to the pharmacological actions of ephedra, and none of the serious adverse events could be directly (causally) related to the use of ephedra containing products. However, it is logical that specific factors such as pre-existing medical conditions (e.g. cardiovascular problems) or concomitant use of sympathomimetic agents (e.g. caffeine) could lead to serious adverse effects and the use of these types of products (including dietary supplements containing ephedra or other stimulants) should be avoided.[108]

Nevertheless, unlike the RAND Report, instead of simply relying on AERs, the CANTOX Report reviewed all other available information related to the safety of ephedra / ephedrine alkaloids. In particular, the authors of the CANTOX Report examined the results of nine (9)

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[102] *Supra*, note 11.

[103] *Id.* at i.

[104] *Id.* at iv.

[105] *Id.*

[106] *Id.* at 61. (Emphasis added).

[107] *Id.* at 65.

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

clinical trials,[109] including the *Boozer* study (a/k/a the "Harvard/Columbia" study).[110] These nine (9) clinical studies are significant because all of them used a randomized, double-blind, placebo-controlled design.[111] Moreover, in these studies ephedrine/ephedra was taken for at least 8 weeks and heart rate, blood pressure, adverse effects, frequency of adverse effects and related tolerability parameters were monitored.[112] As the CANTOX Report found in all of the studies reviewed, no statistically significant differences at doses up to 75 mg/day and placebo were observed in heart rate or blood pressure.[113] Moreover, the *Boozer* study revealed that cardiac arrhythmias did not occur in subjects given 90 mg of ephedrine alkaloids/day versus placebo, although blood pressure was transiently increased and heart rate persistently increased.[114] Therefore, the CANTOX Report concluded that 90 milligrams of ephedra per day would be a safe level for usage, because "no significant increases in frequency of adverse effects or changes in heart rate or blood pressure" occurred at or below this level leading to cardiac arrhythmias.[115]

The CANTOX Report noted that the clinical studies principally tested the efficacy of ephedrine/ephedra in the treatment of obesity, rather than the safety of its use.[116] In addition, the CANTOX Report noted that the clinical trials do not contain significant numbers to test for uncommon adverse effects.[117] In any event, however, the bottom line result according to the

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[109] The clinical studies examined included the following: Pasquali, R. et al., *A controlled trial using ephedrine in the treatment of obesity*, International Journal of Obesity, 9(2): 93-98; Kreiger, D.R., et al., *Ephedrine, caffeine and aspirin promote weight loss in obese subjects*, Trans Assoc Am Physicians 103: 307-312; Astrup, A., et al., *The effect and safety of an ephedrine/caffeine compound compared to ephedrine, caffeine an d placebo in obese subjects on an energy restricted diet. A double blind trial.*, International Journal of Obesity Related Metabolic Disorder 16(4): 269-277; Quaade, F., et al., *The effect of an ephedrine/caffeine combination as a supplement to a weight-reducing diet. A randomized placebo-controlled double-blind trial*, Ugeskrift for Laeger 154(18): 1258-1263; Daly, P.A., et al., *Ephedrine, caffeine and aspirin: Safety and efficacy for the treatment of human obesity*, International Journal of Obesity Related Metabolic Disorders 17(Suppl. 1): S73-S78; Toubro, S., et al., *Safety and efficacy of long-term treatment with ephedrine, caffeine and an ephedrine/caffeine mixture*, International Journal of Obesity Related Metabolic Disorders 17 (Suppl. 1: S69-S72; Nasser, J.A., et al., *Efficacy trial for weight loss of an herbal supplement of Ma huang and guarana*, FASEB J 13(5, Part 2): A874 (Abstract No. 660.8); Boozer, C.N., et al., *Herbal ephedra / caffeine for weight loss: a 6-month randomized safety and efficacy trial*, International Journal of Obesity (2002) 26: 593-604; and Molnar, D., *Effects of ephedrine and aminophylline on resting energy expenditure in obese adolescents*, International Journal of Obesity Related Metabolic Disorders 17(Suppl. 1): S49-S52 (1999).

[110] Boozer, *supra* note 99.

[111] *Supra*, note 11, at 159.

[112] *Id.*

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

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

[115] *Id.*, at i, 158-59.

[116] *Id.* at 145.

[117] *Id.* at 146.

CANTOX Report is that Ephedra is safe when consumed according to the industry recommendations.

C. Other Clinical Studies Have Reached the Same Conclusion as the CANTOX Report.

According to the authors of the CANTOX Report, the *Boozer* study "represents the pivotal clinical study in the safety evaluation of ephedra."[118] Prior ephedra studies involved an 8-week trial that limited any conclusions about long-term safety.[119] However, the *Boozer* 6-month study reported the first long-term clinical trial of an herbal preparation containing ephedrine alkaloids and caffeine in combination.[120] During this trial, patients received either a placebo or 90 milligrams of ephedrine alkaloids per day.[121] The results of the study revealed "no significant change in blood pressure" and no "significant adverse effects" from treatment with herbal ephedra/caffeine.[122] The *Boozer* study concluded that:

> [c]ompared with placebo, the test product produced no adverse effects and minimal side effects that are consistent with the known mechanisms of action of ephedrine and caffeine . . . herbal ephedra / caffeine herbal supplements, when used as directed by healthy overweight men and women in combination with healthy diet and exercise habits, may be beneficial for weight reduction without significantly increased risk of adverse events.[123]

Similar findings have also been reached by the Ephedra Education Council Expert Panel (the "EEC Panel").[124] This panel, convened in response to a request for information regarding Ephedra from the Department of Health and Human Services, consisted of seven medical and science experts from a variety of disciplines.[125] After reviewing all the available information, including the AERs from the FDA, the EEC Panel concluded that the available information:

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[118] *Id.* at 159.

[119] *Boozer*, *supra* note 99, at 594.

[120] *Id.*

[121] *Id.* at 595.

[122] *Id.* at 602. (Emphasis added).

[123] *Id.* at 602-3. (Emphasis added).

[124] *See* Consensus Statement of the Ephedra Education Council Expert Panel, August, 2000.

[125] *Id.*

[d]oes not demonstrate an association between the use of dietary supplements containing ephedrine alkaloids and serious adverse events when used according to industry recommendation for ephedra product.[126]

Additionally, the *Kimmel* study concluded that "the use of dietary supplements containing ephedrine alkaloids does not increase the risk of seizures, strokes or heart attacks."[127] Several other studies have likewise concluded that ephedra / ephedrine-containing products are safe when used according to recommended dosages.[128]

Despite these significant findings, the FDA continues to rely on the RAND Report and its faulty based AERs to support its proposed regulations. United Metabolic believes that the conclusions of the CANTOX Report, including the *Boozer* study, provide more substantive and relevant analyses and should be given further consideration by the FDA prior to instituting any proposed rules or regulations on ephedra or ephedrine alkaloids. These studies provide direct contradictory evidence to any assertion by the FDA that ephedra/ephedrine poses a "significant or unreasonable risk of illness or injury. As previously addressed, failure to acknowledge the findings of the CANTOX Report and the *Boozer* study would certainly provide a basis for a reviewing court to determine that the FDA's regulations were in fact, "arbitrary and capricious" in violation of the APA.

IV. FDA's Proposed Warning Label Cannot be Evenly Applied as to Mail Order Dietary Supplement Suppliers, Such as United Metabolic and Thus, Is Arbitrary and Capricious.

As stated previously, United Metabolic sells dietary supplements containing ephedrine alkaloids through the use of mail order. Here, the consumer does not purchase the product in the same manner as one would purchase an over-the-counter ("OTC") supplement. Instead, the interested consumer simply mails to United Metabolic the order form that is included in our advertising. This order form requires the consumer to provide to us the pertinent information such as name and address, as well as, the amount of product to be ordered and the price. In the alternative, an interested consumer may simply call a toll free telephone number and place an order for our products. It is important to recognize that, in the mail order situation, the consumer has already made an assessment of the benefits versus any risks at the point of purchase (i.e. the filling out of

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

[127] Kimmel, S., *Background risk of seizures, strokes, and myocardial infarction compared to the incidence of such events in persons consuming dietary supplements containing ephedrine alkaloids*, (2000).(Emphasis added);

[128] *See* Greenway, F.L., *The safety and efficacy of pharmaceutical and herbal caffeine and ephedrine use as a weight loss agent*, International Association for the Study of Obesity, Obesity Reviews, (2001) 2: 1999-211 (concluding that the weight loss benefits of these products "appear to outweigh the small associated risks); de Jonge, L., *Safety and efficacy of an herbal dietary supplement containing caffeine and ephedra for obesity treatment*, Pennington Biomedical Research Center, Louisiana State University, October 2001; and Morgenstern, L.B., et al., *Use of Ephedra-containing products and risk for hemorrhagic stroke*, Neurology 2003; 60:132-135 (concluding that Ephedra is not associated with increased risk for hemorrhagic stroke, except possibly at higher doses). (Emphasis added).

the mail order form or calling the toll free telephone number). This is different from the OTC point of purchase where a prospective consumer has numerous forms of product to choose from and must read the various product information for each of the products before any purchase. Based on these facts, it is clear that the FDA's proposed warning label cannot be evenly applied as to the mail order dietary supplement market.

According to the FDA's proposal, the following warning statement would appear on the "principal display panel of the product:"

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

In the context of the mail order dietary supplements, the "principal display panel" would be the front page of any product literature used by the manufacturer to advertise its product. For instance, United Metabolic provides a pamphlet that describes a given product and details the benefits and risks of using its product. Under the FDA's proposal, the outside cover page of this pamphlet would be required to include the foregoing warning. United Metabolic believes that such placement of the warning is unreasonable as applied to the mail order dietary supplement suppliers.

United Metabolic appreciates the FDA's desire to have a reasonable warning statements regarding products at the point of purchase. However, United Metabolic believes that the FDA's requirement of the proposed warning on the "principal display panel" effectively singles out the mail order dietary supplement supplier. Requiring the mail order supplier to include the above warning on the cover page of its product advertising would not be equivalent to the front label on an OTC dietary supplement. As mentioned above, in the mail order context, the consumer has already made the informed decision regarding benefits versus risks at the point of purchase (e.g. filling out the order form or calling the toll free telephone number). On the other hand, with respect to OTC supplements, the consumer must review all the available products and their respective labels *prior* to reaching the point of actual purchase. United Metabolic believes this essential difference represents an unreasonable approach to any proposed warning labels that would not withstand a court's review under the "arbitrary and capricious" standard.

In lieu of the "principal display panel," United Metabolic recommends the following alternative for the placement of any additional warning labels that the FDA may require. In the mail order context, the location of the warning label should be either above the mail order form used by the consumer to order the product or above the toll free telephone number that the consumer may call to order the product. In United Metabolic's view, these alternative locations for mail order dietary supplements seem more reasonable and equivalent to the product label in the OTC context. In both this alternative location and the product label in the OTC supplement, the

warning label is more likely to be read by the consumer at the point of purchase. United Metabolic believes that this alternative approach accomplishes the FDA's intended goal of warning at the point of purchase but in a more even and reasonable manner.

With reference to the specific language of the proposed warning, United Metabolic appreciates the FDA's intent to warn the prospective consumer of all potential side effects from the use of dietary supplements containing ephedrine alkaloids. However, United Metabolic believes that its past and current warning labels more than adequately provide the necessary information for the consumer. In fact, United Metabolic believes that its current warning statements regarding dietary supplements are even more stringent than required by the FDA in its proposed warnings.

For example, prior to March 19, 2003, the product label information contained on the packaging for Betadrene, manufactured by United Metabolic, read as follows:

> **Warning:** Do not use if you are pregnant or nursing. Consult a physician before using this product if you have, or have a family history of heart disease, thyroid disease, diabetes, high blood pressure, recurring headaches, depression or other psychiatric condition, glaucoma, difficulty urinating due to prostate enlargement, seizure disorder. Do not use if you are using a monamine oxidase inhibitor (MAO) or any other dietary supplement, prescription drug or over-the-counter drug containing ephedrine, pseudoephedrine, or phenylpropanolamine. Exceeding recommended dosage may cause serious adverse side effects including heart attack and stroke. Discontinue use and call a physician immediately if you experience rapid heartbeat, dizziness, severe headache, shortness of breath, or other similar symptoms. Individuals who are allergic or hypersensitive to ephedrine or caffeine should avoid the use of this product. Not for use by individuals under the age of 18. Maximum recommended dosage of ephedrine alkaloids for a healthy adult is no more than 100 mg. in a 24 hour period for not more than 12 weeks. Improper use of this product may be hazardous to your health. **KEEP OUT OF REACH OF CHILDREN**

Although United Metabolic still believes the foregoing warning statement fully and accurately describes any and all potential adverse effects from the use of a dietary supplement containing ephedrine, United Metabolic has recently changed the warning labels its products carry. Thus, as of March 19, 2003, Betadrene has the following warning on its product label:

> **WARNING: NOT FOR USE BY INDIVIDUALS UNDER THE AGE OF 18 YEARS. DO NOT USE IF YOU ARE PREGNANT OR NURSING.** CONSULT A PHYSICIAN OR LICENSED QUALIFIED HEALTH CARE PROFESSIONAL BEFORE USING THIS PRODUCT IF YOU HAVE, OR HAVE A FAMILY HISTORY OF HEART DISEASE, THYROID DISEASE, DIABETES, HIGH BLOOD PRESSURE, RECURRENT HEADACHES, DEPRESSION OR OTHER PSYCHIATRIC CONDITION, GLAUCOMA, DIFFICULTY IN URINATING, PROSTATE ENLARGEMENT, OR SEIZURE DISORDER, OR IF YOU ARE USING A PRESCRIPTION DRUG OR OVER-

THE-COUNTER DRUG CONTAINING EPHEDRINE, PSEUDOEPHEDRINE, OR PHENYLPROPANOLAMINE (INGREDIENTS FOUND IN CERTAIN ALLERGY, ASTHMA, COUGH/COLD, AND WEIGHT CONTROL PRODUCTS). DO NOT EXCEED RECOMMENDED SERVING. EXCEEDING RECOMMENDED SERVING MAY CAUSE SERIOUS ADVERSE HEALTH EFFECTS, INCLUDING HEART ATTACK AND STROKE. DISCONTINUE USE AND CALL A PHYSICIAN OR LICENSED QUALIFIED HEALTH CARE PROFESSIONAL IMMEDIATELY IF YOU EXPERIENCE RAPID HEARTBEAT, DIZZINESS, SEVERE HEADACHE, SHORTNESS OF BREATH, OR OTHER SIMILAR SYMPTOMS. INDIVIDUALS WHO CONSUME CAFFEINE WITH THIS PRODUCT MAY EXPERIENCE SERIOUS ADVERSE HEALTH EFFECTS. INDIVIDUALS WHO ARE SENSITIVE TO THE EFFECTS OF CAFFEINE SHOULD CONSULT A LICENSED HEALTH CARE PROFESSIONAL BEFORE CONSUMING THIS PRODUCT. IN CASE OF ACCIDENTAL OVERDOSE, SEEK PROFESSIONAL ASSISTANCE OR CONTACT A POISON CONTROL CENTER IMMEDIATELY. AVOID ALCOHOL WHILE TAKING THIS PRODUCT.

THE MAXIMUM RECOMMENDED DOSAGE OF EPHEDRINE FOR A HEALTHY ADULT HUMAN IS 100 MILIGRAMS IN A 24-HOUR PERIOD FOR NOT MORE THAN 12 WEEKS. IMPROPER USE OF THIS PRODUCT MAY BE HAZARDOUS TO A PERSON'S HEALTH. EXCEEDING RECOMMENDED SERVING WILL NOT IMPROVE RESULTS.

THIS PRODUCT HAS 25 MILLIGRAMS OF CONCENTRATED EPHEDRINE GROUP ALKALOIDS PER SERVING IN THE FORM OF HERBAL EXTRACTS.

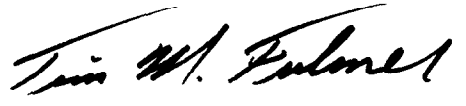
It is clear that the foregoing product labeling, as used by United Metabolic, fully satisfies the intentions of the FDA with its proposed warning labels. Moreover, United Metabolic's current labeling fully and accurately describes the potential for adverse effects from the use of dietary supplements containing ephedrine alkaloids. Nevertheless, excepting the recommendation described above regarding location, United Metabolic fully intends to comply with the intent of the proposed FDA regulations, whether or not such regulations become effective.

V. Conclusion

For the above reasons, United Metabolic respectfully requests that the Agency terminate the entire rulemaking process associated with dietary supplements that contain ephedrine alkaloids. In the alternative, United Metabolic requests that the Agency give further considerations to the numerous other studies that have shown the safety of dietary supplements containing ephedra or ephedrine when used at their recommended dosages. In addition, United Metabolic agrees with

the call for future controlled clinical studies regarding the use of dietary supplements containing ephedra or ephedrine. Moreover, United Metabolic will assume a roll of participating in future studies of the safety and efficacy of ephedrine based products. Finally, United Metabolic requests that with respect to any labeling changes as may be required by the FDA for mail order dietary supplement suppliers, such as United Metabolic, additional consideration should be given to the placement of warnings in order to more equally address the point of purchase concerns of the FDA.

Respectfully submitted,



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