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VIA HAND-DELIVERY

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

Re. Dietary Supplements Containing Ephedrine Alkaloids
[Docket No. 00N-1200]

Dear Sir or Madam:

On behalf of Metabolife International, Inc. ("Metabolife"), we are hereby submitting these comments to the docket recently established by the Food and Drug Administration ("FDA" or "Agency") to address the new adverse event reports ("AERs") that allegedly are related to dietary supplements that contain ephedrine alkaloids.¹ Metabolife, which was officially established in 1995, is dedicated to the ethical formulation of dietary supplement products according to sound scientific principles. Metabolife's flagship product, Metabolife 356[®], has, in a few years, become one of the best selling dietary supplement products in the United States. Metabolife manufactures all of its products in accordance with stringent standard operating procedures ("SOPs") that comply with FDA good manufacturing practices ("GMPs").

In the instant case, we believe the Agency's attempt to subject dietary supplements that contain ephedrine alkaloids to unprecedented regulatory controls is, and has been, based upon a fundamental misconception regarding the safety data applicable to such products and the role and validity of AERs. In the absence of credible scientific support, 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 based virtually entirely upon AERs that uniformly have been deemed unreliable by independent third-parties as well as the Agency itself.

FDA's stubborn insistence on AER reliance to support this rulemaking directly contravenes the conclusions of the General Accounting Office ("GAO"), Congress, the Small Business Administration ("SBA"), and the Agency itself. As explained herein, we believe the new AERs are subject to the same criticisms previously identified by these entities - and

¹ Due to the fact that this new docket constitutes a continuation of the issues previously addressed by the Agency in its original docket dedicated to this issue [Docket No. 95N-0304], we hereby incorporate by reference the entire original docket into this new docket.

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therefore are incapable of scientifically supporting FDA's proposed rulemaking regarding dietary supplements that contain ephedrine alkaloids.

We believe that FDA'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"),² as it involves an extra-statutory mechanism not authorized by Congress. We further believe that, based upon the failure of the AERs to support FDA's contentions, there is no credible scientific support for FDA's rulemaking on this issue – and that any such rulemaking would be found to be "arbitrary and capricious" and in violation of the Administrative Procedure Act ("APA"). Accordingly, we respectfully request that the Agency immediately withdraw all of the provisions in its proposed rule of June 4, 1997³ (the "Ephedra Proposal") - and immediately terminate this rulemaking process.

In lieu of Agency rulemaking, Metabolife urges the Agency to adopt the industry-proposed guidance document, prepared as a draft Compliance Policy Guide ("CPG"), that was previously provided to the Agency. (See Attachment A). This proposed CPG establishes reasonable restrictions on ephedrine-containing dietary supplement products, and may be applied by the Agency on a product-by-product basis if certain companies refuse to comply.

Specifically, the CPG would: (1) establish a limitation on serving size (25 mg ephedrine alkaloids per serving) and overall daily consumption (100 mg ephedrine alkaloids); (2) require labels with warnings and content disclosures; (3) prohibit the sale of ephedrine-containing dietary supplement products to minors; (4) prohibit claims that such products may be useful to achieve an altered state of consciousness, euphoria, or as a "legal" alternative for an illicit drug; and (5) if the product contains caffeine, require a disclosure of caffeine levels. Metabolife encourages the Agency to adopt this proposed industry standard.

In this regard, Metabolife believes cooperation between the Agency and regulated industry is essential. To that end, Metabolife has been actively involved in monitoring the science surrounding dietary supplement products containing ephedrine alkaloids in order to help establish meaningful standards for the dietary supplement industry. As part of its proactive efforts to help establish a reasonable regime for regulating dietary supplements that contain ephedrine alkaloids, Metabolife has requested a meeting with Commissioner Henney in order to discuss ways in which the FDA and regulated industry can work together for consumer benefit.

In addition to our substantive objections to the proposed rule, we believe that the Agency has denied regulated industry a fair opportunity to review the administrative record due to the stringent time-frames granted regulated industry to submit comments to the Agency. Specifically, given the extensive number of AERs, and the years in which FDA had to analyze the AERs, we believe the regulatory process has been structured by the Agency to

² 21 U.S.C.A. §§ 321-97 (West 2000).

³ 62 Fed. Reg. 30678 (June 4, 1997).

deny regulated industry an opportunity to fairly respond to the new AERs and the new analyses conducted by the Agency.

At a minimum, we believe a comment period of 180 days (with 180 day advance notice of the termination of the comment period) should have been granted to enable regulated 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 regulated industry with sufficient time to assert its position and apply its legal right to comprehensively review the administrative record.⁴

Finally, we reserve the right to submit additional comments, data, and information to the Agency prior to the new September 30, 2000 comment period deadline (which was announced by the Agency on June 8, 2000).⁵ We expect to submit extensive scientific analyses of the new AERs and FDA’s evaluation of them, along with additional data that support the safety profile of dietary supplements that contain ephedrine alkaloids. Moreover, to the extent FDA’s proposed rule does not rely upon widely condemned AER analyses, the next submission will evaluate any non-AER related evidence the Agency can identify or produce.

I. Positive Safety Profile of Dietary Supplements that Contain Ephedrine Alkaloids

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 use-data recently compiled by Arthur Anderson LLP for the American Herbal Products Association (“AHPA”). As explained below, the use-data clearly supports the overwhelmingly positive safety profile of these products.

Fourteen leading companies that sold dietary supplements containing ephedrine alkaloids from 1995 to 1999 responded to the survey. The survey indicates that 1999 sales of dietary supplements containing ephedrine alkaloids increased to more than 3 billion servings. Each

⁴ The Agency’s last-minute grant of an extension until September 30, 2000 to submit additional comments does not rectify the inherent unfairness and inadequacy of the comment period established by the Agency. FDA has continually limited the amount of time available for the dietary supplement industry to analyze the data and evidence produced against it, and grudgingly has granted piecemeal extensions that still do not provide regulated industry even one-third of the time the Agency had to evaluate the applicable data and information. In addition, by granting piecemeal extensions rather than one extension identified in advance, regulated industry has been denied due process. Specifically, the scientific review and evaluation process has been unfairly manipulated as planning and coordination activities have been continually subject to revision. The Agency is surely aware that the grant of six 30-day comment period extensions is not the same as the establishment of an 180-day comment period – because planning and coordination is limited when timetables are constantly altered.

⁵ See Letter from Joseph A. Levitt, Director, Center for Food Safety and Applied Nutrition (“CFSAN”), to the Dietary Supplement Community (June 8, 2000).

of the fourteen companies employed a system to collect reports of serious adverse events allegedly relating to consumption of its products. Despite the sale of over 3 billion servings, only 25 alleged “serious adverse events” were reported during this time period – reflecting 8.1 adverse event reports per billion servings.

The above use-data compares favorably with virtually any food or dietary supplement product sold in the United States – and clearly does not evidence a safety problem associated with dietary supplements that contain ephedrine alkaloids.⁶

II. FDA’s Continued Reliance on AERs, Despite Widespread Condemnation by the GAO, SBA, and the Agency Itself, Is “Arbitrary and Capricious” in Violation of the APA.

A. Background

Despite the positive safety profile associated with dietary supplements that contain ephedrine alkaloids, FDA continues to pursue its misguided course by re-emphasizing the importance of AERs and by citing new AERs that allegedly support its position. FDA fails to realize, however, that unreliable AERs cannot be turned into reliable sources of information simply by counting more of them. The initial batch of AERs relied upon by the Agency to support its proposed rule was widely condemned, and the new batch of AERs are no different in magnitude or relevance. FDA’s attempt to create gold from straw cannot succeed, regardless of the amount of straw the Agency collects.

The administrative record provides no science-based evidence that supports FDA’s proposed restrictions. In promulgating the proposed rule, FDA relied almost exclusively on anecdotal evidence contained in approximately 800 AERs that were collected by FDA from 1993 until June 1997. FDA’s reliance on AERs in this context was particularly egregious given that FDA has historically treated AERs as unreliable. In addition, FDA failed to review the AERs to remove incomplete and inaccurate reports. This failure was so egregious that the administrative record for the Ephedra Proposal contained irrelevant reports, such as the following:

- two reports of deaths due to automobile accidents (AERs 9505, 11015),
- two reports of attempted suicide / suicide (AERs 10338, 11012),
- a report of a person who shot and killed a store clerk (AER 11096),

⁶ Many other foods, such as peanuts, strawberries, fish, eggs, dairy products, soy products, and wheat, are subject to significantly more adverse reactions than dietary supplements that contain ephedrine-alkaloids – and such reactions to conventional foods are often serious, potentially resulting in seizures and occasionally death.

- a report of a woman who got pregnant although she was using Norplant (AER 10258), and
- a report of a 75 year old woman who began menstruating (AER 10338).

In the face of overwhelming criticism, even from neutral parties such as the GAO and the SBA, FDA was compelled to backtrack on its initial proposal. On April 3, 2000, FDA withdrew the provisions of the proposed rule regarding dosage level and duration of use, conceding that:

In light of the GAO's conclusions, comments from others on the ephedrine alkaloids proposal, and having further considered issues related to the proposed dietary ingredient level and the duration of use limit, FDA believes that these aspects of its proposed approach to regulating these products should be reassessed.⁷

Although we support FDA's decision to withdraw these provisions, we believe the Agency is now also obligated to withdraw the remaining portions of the proposed rule as well (*i.e.* the caffeine/ephedrine alkaloid restrictions and the proposed warning statements).

B. Scientific Invalidity of AERs

The Agency's continued effort to rely upon AERs to support this rulemaking is in direct contravention of criticisms from the GAO. In July, 1999, the GAO issued a report entitled "Dietary Supplements: Uncertainties in Analyses Underlying FDA's Proposed Rule on Ephedrine Alkaloids" (the "GAO Report"). FDA's recent efforts to continue this rulemaking evidences a total disregard of this report.

By way of background, the U.S. House of Representatives Committee on Science asked the GAO, on May 12, 1998, to conduct the following analysis of FDA's proposed rule regarding dietary supplements that contain ephedrine alkaloids:

1. Please carefully review the AERs used by FDA to establish dosage level and frequencies for diet products using ephedrine alkaloids. What is the quality of these AERs in terms of data, analysis of all relevant and contributing factors, analysis of the product identified as that consumed in each case, and so forth?
2. What internal guidance does FDA have on the use of AERs as the basis of regulation? Are there rules in place that clarify how AERs can properly be used? In prior cases where AERs were used, what role did they play in the rule-making?

⁷ 65 Fed. Reg. 17474, 17475 (Apr. 3, 2000).

3. What is the quality of the cost-benefit analysis performed by FDA? Did they engage in the proper job of reaching out to potentially affected parties as well as analyzing the impacts of the proposed rule as required in the Regulatory Flexibility Act?
4. In light of your findings in response to question three, should the FDA have complied with the requirements of the Unfunded Mandates Reform Act?⁸

Importantly, as demonstrated by the above questions, the GAO was not asked to review the restrictions proposed by FDA on caffeine/ephedrine alkaloid combinations – and was not asked to review the labeling requirements proposed by the Agency. The GAO ultimately concluded that the two substantive aspects of the proposed rule that Congress asked it to review (*i.e.* dosage level and frequency restrictions) were not scientifically supported. The GAO concluded that FDA's analysis relied on poorly documented reports of adverse events:

Specifically, the agency 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. FDA also used these AERs to determine the number of serious events that could be attributed to the dietary supplements and the expected benefits that would arise if the proposed rule were implemented. However, FDA did not document which AERs it determined to be serious. Moreover, it did not establish criteria to determine which events were serious and did not perform any reliability assessments of its analyses.⁹

Moreover, the GAO concluded that AERs are inherently unreliable because 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

⁸ Letter from the U.S. House of Representatives Committee on Science to the GAO (the "House Letter"), dated May 12, 1998. Notably, the GAO recently reiterated its concerns with FDA's proposed rule on dietary supplements containing ephedrine alkaloids. *See generally* GAO Report: Regulatory Reform: Procedural and Analytical Requirements in Federal Rulemaking (June 8, 2000).

⁹ GAO Report, at 8.

spontaneous reporting, (4) an estimation of population exposure, and (5) that the quality of the data received was generally poor.¹⁰

The GAO also noted that the “inherent weaknesses of AERs,” and FDA’s reliance on them, added uncertainty to FDA’s proposed rule.¹¹ Moreover, the GAO noted that the AERs “lacked important information,”¹² and that the AERs raise significant questions about the “causal relationship between ingestion of the implicated product and the adverse events observed.”¹³

In addition to ignoring the GAO’s concerns, FDA has also ignored statements by the Agency itself that criticized AER reliance. For example, the Director of FDA’s Office of Nutritional Products, Labeling and Dietary Supplements was recently quoted as stating the following with regard to AERs:

The data 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, said Dr. Christine Lewis, director of the FDA’s Office of Nutritional Products, Labeling and Dietary Supplements.¹⁴

Moreover, FDA’s Website posts a disclaimer cautioning that AERs “cannot be used to estimate the rate of occurrence [of an adverse event] in a population,” and that “there is no certainty that a reported adverse event can be attributed to a particular product.”¹⁵

These statements are not surprising and are entirely consistent with FDA’s statements regarding the AER process – including statements related to FDA’s drug adverse event database. For example, at a meeting of the Psychopharmacological Drugs Advisory Committee meeting discussing potential suicide risks associated with antidepressants, Dr. Paul Leber, Director of the Division of Neuropharmacological Drug Products stated: “a large volume of reporting to a spontaneous adverse reaction system is not in of itself a reliable index of a drug’s risk.”¹⁶ Dr. Leber acknowledged that the number of adverse event reports associated with a product depends on multiple factors, such as how recently the drug

¹⁰ See *id.* at 35-36.

¹¹ See *id.* at 10.

¹² *Id.* at 11.

¹³ *Id.* at 13.

¹⁴ Tracy Wheeler & Jim Quinn, *Herbal Products Cause Ill Effects: Natural Remedies Can Prove Deadly*, Akron Beacon Journal, May 9, 2000.

¹⁵ See *The Special Nutritionals Adverse Event Monitoring System*, FDA CFSAN, Office of Special Nutritionals, <http://vm.cfsan.fda.gov/~dms/aems.html> (governing adverse event reports associated with dietary supplements, infant formulas, and medical foods).

¹⁶ Meeting Transcript, Psychopharmacological Drugs Advisory Committee, September 20, 1991, at 125.

was introduced into the marketplace, the drug's market share, and publicity.¹⁷ Therefore, Dr. Leber stated that risk assessments are generally only deemed reliable if they are derived from clinical sources of evidence that allow a comparison of the incidence and the intensity of the events in the presence and absence of the drug at issue.¹⁸

Moreover, during the House Committee on Government Reform Hearing on May 27, 1999, regarding the accuracy of FDA's monitoring of supplements like ephedra, three primary problems with the accuracy and reliability of FDA's dietary supplement AER system were identified:

- Causality was not established – FDA does not conduct significant follow-up after AERs are reported in order to confirm that the event was actually caused by a dietary supplement.
- Brand and corporate names are identified without confirmation that the product caused the event.
- Incorrect information is not purged.¹⁹

Joseph A. Levitt, the Director of FDA's Center for Food Safety and Applied Nutrition ("CFSAN"), testified that:

- The AER system serves to augment, not replace, other systems and tools for determining safety of products.
- Limitations of the AER system include: underreporting, report quality, adverse event recognition, biases, and estimation of population exposure.²⁰

¹⁷ See *id.* The reliability of AERs is subject to further dispute as the number of AERs submitted to the Agency has been influenced by factors unrelated to product safety. Regulated industry has charted the number of AERs concerning ephedrine alkaloid dietary supplements reported to FDA between January 1993 and August 1997. Three of the most significant increases in AER reports occurred immediately after the dietary supplements received negative publicity on February 28, 1995 (FDA Press Release), April 10, 1996 (FDA Press Release), and July 9, 1996 (Montel Williams Telecast – irresponsibly entitled "Ephedrine – The Legal Drug That's Killing Our Kids").

¹⁸ See Meeting Transcript, Psychopharmacological Drugs Advisory Committee, September 20, 1991, at 125.

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 2-3.

²⁰ 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 7-10.

In addition, FDA's past practices regarding AERs corroborate the Agency's prior statements that AERs are unreliable. During prior rulemakings, FDA relied upon AERs only in conjunction with reliable studies.²¹

Further, the SBA,²² in its February 3, 1998 comments that criticized the FDA's use of AERs, noted that during this very rulemaking FDA itself acknowledged that AERs are unreliable. Based upon FDA's own caveats, the SBA found that "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."²³ Moreover, the SBA noted that with regard to the Agency's cost-benefit analysis, the Agency's alleged benefits that would arise from the rule were questionable as "the [A]gency's claims regarding lives saved and the elimination of serious injuries are unsubstantiated."²⁴ Accordingly, the SBA concluded that "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."²⁵

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

It is well-established that pursuant to the APA courts may set aside an agency regulation that is "arbitrary and capricious" or substantially unsupported by the factual record.²⁶ Although a reviewing court may not substitute its judgment for that of the agency under this standard, a reviewing court may intervene to ensure that the agency has "examine[d] the relevant data and articulate[d] a satisfactory explanation for its action."²⁷ A reviewing court, however, may

²¹ See, e.g., 44 Fed. Reg. 37212 (June 26, 1979) (relying upon AERs in addition to other studies in determining whether to regulate Yellow No. 5); 42 Fed. Reg. 6835, 6835-36 (describing the AERs and multiple clinical studies upon which FDA based its regulation of Yellow No. 5); 49 Fed. Reg. 13679 (Apr. 6, 1984) (scaling back the severity of a 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).

²² The Office of Chief Counsel for Advocacy of the SBA was created in 1976 to represent the views and interests of small businesses in federal policy-making activities. The Chief Counsel participates in rulemakings only when deemed to be necessary to ensure proper representation of small business interests.

²³ Letter from SBA, to FDA, regarding the Ephedra Proposal, dated Feb. 3, 1998, at 5.

²⁴ *Id.* at 6.

²⁵ *Id.* at 7.

²⁶ See 5 U.S.C.A. § 706(2) (West 2000); *Dickinson v. Zurko*, 527 U.S. 150, 164 (1999) (holding that absent an exception, a court will not uphold factual findings made by any agency, including the United States Patent and Trademark Office, if the findings are "arbitrary and capricious" or insufficiently "bound up with a record-based factual conclusion"); *Motor Vehicle Mfrs. 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).

²⁷ *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* for this proposition and holding

undo an agency's action if the agency has failed to provide a reasoned explanation for the action, or if the administrative record belies the agency's conclusion.²⁸ The test is whether "a reasonable mind might accept a particular evidentiary record as adequate to support a conclusion."²⁹ For the reasons explained below, FDA's administrative record is inadequate to support FDA's proposal to regulate dietary supplements containing ephedrine alkaloids.

The additional 270 AERs that have recently been added to the administrative record necessarily suffer from the same deficiencies as the initial 800 – because AERs are inherently unreliable. In light of the GAO's and the SBA's criticisms, FDA should not be permitted to rely primarily upon the faulty data contained in the AERs to support its prohibition on caffeine/ephedrine alkaloid combinations or any new restrictions on dosage level or duration of use, if such restrictions are subsequently proposed. If FDA persists on its current path, it is beyond peradventure that a reviewing court would set aside the ephedrine alkaloid rulemaking as "arbitrary and capricious."

Given the "arbitrary and capricious" standard, courts are compelled to find that any regulation or agency decision that is inadequately supported by evidence and scientific data in the administrative record is "arbitrary and capricious." For example, courts have set aside rulemakings as "arbitrary and capricious" when the scientific evidence has had the following deficiencies:

- FDA's administrative record for a rule (1) did not contain evidence that demonstrated a cause and effect relationship between AERs and the substance at issue, (2) contained a government report that failed to support FDA's proposed restrictions, and (3) contained a telephone survey that failed to provide a risk assessment regarding the product at issue.³⁰
- The Occupational Safety and Health Administration's ("OSHA's") 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 limits, and (3) supported its assumption that the risk of adverse events would decrease as exposure to benzene decreased.³¹

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).

²⁸ See *County of Los Angeles*, 192 F.3d at 1021.

²⁹ *Zurko*, 527 U.S. at 162 (citations omitted).

³⁰ See *Council for Responsible Nutrition v. Goyan*, 1978-80 FDLI Jud. Rec. 595 (D.D.C. 1980).

³¹ See generally *Industrial Union Dep't v. American Petroleum Inst.*, 448 U.S. 607 (1980).

- The Environmental Protection Agency's ("EPA's") administrative record for a rule contradicted its proposed rule because one of EPA's own staff papers acknowledged that the indicator, which EPA chose to regulate coarse particulate matter ("PM"), was over-inclusive.³²
- FDA's administrative record for a rule contained a scientifically flawed survey, upon which FDA relied to promulgate the regulation at issue.³³
- HHS's administrative record for a rule contained statistics that had been compiled for a limited purpose, and HHS relied upon these statistics to promulgate the rule at issue, even though the statistics were not applicable to the rule at issue.³⁴

These cases are all directly applicable to FDA's proposed rule on dietary supplements containing ephedrine alkaloids because, in the instant case, the "scientific evidence" relied upon by the Agency is even weaker than the evidence in the above cases. In the instant case, FDA is relying almost entirely on discredited AERs to provide the "scientific support" for its rulemaking. Similar to the examples above, such weak evidence is insufficient to support restrictive rulemaking and would be set aside as "arbitrary and capricious."

Notably, in two of the cases mentioned above, *American Trucking* and *County of Los Angeles*, the D.C. Circuit held that rules promulgated by EPA and HHS, respectively, were "arbitrary and capricious" because they were unsupported by substantial evidence and were contradicted by the agency's own reports.³⁵ Similar agency actions, which are unsupported by substantial evidence and ignore reliable third-party reports in the record, or other criticisms, are equally egregious.

Courts have continually made it clear that criticisms of an agency's action simply cannot be "swept under the rug" to justify an agency's continued pursuit of a predetermined course of action.³⁶ Courts have ruled that certain agency actions were "arbitrary and capricious," or

³² See *American Trucking v. EPA*, 175 F.3d 1027, 1053-54 (D.C. Cir. 1999).

³³ See *Almay v. Califano*, 569 F.2d 674, 682-83 (D.C. Cir. 1978).

³⁴ See *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 that the same rule was "arbitrary and capricious" on the same grounds); *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 (3^d 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").

³⁵ See *County of Los Angeles*, 192 F.3d at 1021; *American Trucking*, 175 F.3d at 1054.

³⁶ See *Seattle Audubon Society v. Moseley*, 798 F. Supp. 1473, 1479-82 (W.D. Wash. 1992) (holding that the United States Forest Service's approval of an environmental impact statement ("EIS") was "arbitrary and capricious" because the agency "swept" a contradictory report submitted by the United States Fish and Wildlife Service "under the rug").

have condemned certain agency actions, where an agency has ignored reliable third-party reports and/or other criticisms.³⁷

In the present case, FDA has blatantly ignored the central holding of the GAO Report – that AERs provide inadequate evidentiary support for the regulation of dietary supplements containing ephedrine alkaloids. In no uncertain terms, the GAO criticized FDA’s use of AERs to restrict dosage levels and duration of use because AERs are inherently unreliable. Nevertheless, FDA ignored the holding’s application to the prohibition on caffeine/ephedrine alkaloid combinations, which is also based upon AERs. Moreover, FDA has perpetuated its error by citing more inherently unreliable AERs to support its position.

There is little doubt that a court would find FDA’s attempt to by-pass the concerns of the GAO, an unbiased third-party, as well as similar concerns expressed by Congress and the SBA, to be particularly egregious. FDA’s insistence on relying upon the faulty data contained in the AERs demonstrates an unwillingness to veer off its predetermined course of action, despite direct evidence that contradicts its position. Accordingly, in the instant case a reviewing court would set aside FDA’s final rulemaking as “arbitrary and capricious.”

III. There Is No Scientific Evidence that Caffeine/Ephedrine Alkaloid Combinations Pose a Health or Safety Concern, and Therefore FDA’s Proposed Prohibition of Such Combinations Is also “Arbitrary and Capricious.”

A. FDA Has Fundamentally Misconstrued the GAO Report and Has Ignored Its Relevance to the Proposed Caffeine/Ephedrine Alkaloid Restrictions.

Based upon the critical GAO Report, the Agency recently agreed, in a Federal Register notice, to withdraw the dosage level and frequency restrictions in its proposed rulemaking.³⁸ The Agency, however, fundamentally misconstrued the GAO Report by refusing to withdraw the caffeine/ephedrine alkaloid restrictions and mandatory warnings proposed in

³⁷ See, e.g., *A.L. Pharma, Inc. v. Shalala*, 62 F.3d 1484, 1492 (D.C. Cir. 1995) (holding that FDA’s promulgation of a final rule was “arbitrary and capricious” because 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) (holding that the FAA’s disregard of a report from the National Park Service, which 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) (holding that an 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 a treating physician); *Sierra Club v. United States Army Corps of Engineers (“COE”)*, 701 F.2d 1011, 1032-33 (2d Cir. 1983) (holding that the COE’s approval of an EIS and issuance of a dredge and fill permit was “arbitrary and capricious” because the agency failed to address criticisms from several other agencies and to consider a contradictory biological study in the administrative record); *Cobell v. Babbitt*, 1999 WL 1581470, *52-53 (D.D.C. Dec. 21, 1999) (condemning the Department of Interior for ignoring congressional directives and criticisms from the GAO, the Inspector General, and several other agencies by continuing to mismanage the individual Indian money trusts).

³⁸ See 65 Fed. Reg. at 17474-75.

the proposed rulemaking. In the instant case, although the GAO was only asked to review the reliability of the AERs used to support dosage level and duration of use limits, the GAO's criticisms, like the criticisms of the SBA and FDA, apply universally to the use of AERs relating to dietary supplements that contain ephedrine alkaloids.

With regard to the caffeine/ephedrine alkaloid proposed restrictions, FDA acknowledged in this recent Federal Register notice that the restrictions are based upon AERs. Specifically, the FDA stated:

FDA proposed . . . to require that no ingredient, or ingredient that contains a substance, that has a known stimulant effect (e.g. sources of caffeine, yohimbine) may be included in a dietary supplement that contains ephedrine alkaloids. FDA proposed this provision in response to the many adverse events that had been reported to the agency.³⁹

Based upon the express acknowledgement that the caffeine/ephedrine alkaloid proposed restrictions are based solely upon AERs, FDA is obligated to withdraw these provisions as well. To continue to pursue these restrictions in the face of Congressional and GAO criticism regarding over-reliance upon AERs would constitute an affront to the scientific process and would be "arbitrary and capricious" in direct violation of the APA. GAO's scientific criticisms regarding reliance upon AERs apply to the use of AERs relating to dietary supplements that contain ephedrine alkaloids for any reason – and are not limited to the use of such AERs to establish dosage levels and frequency levels.

FDA's strained reading of the GAO Report would result in the untenable situation where AERs would not be relied upon to establish dosage level and frequency levels (due to their scientific unreliability), but would be relied upon for establishing caffeine/ephedrine alkaloid restrictions – even though the exact same AERs are utilized. Given the widespread conclusion that the AERs are unreliable, they should clearly be deemed unreliable for any use. The only reason the GAO did not expressly criticize the use of AERs to support the caffeine/ephedrine alkaloid restrictions is that Congress did not instruct the GAO to review the caffeine/ephedrine alkaloid issue. FDA's attempt to bypass the GAO's concerns, by relying upon faulty data, should be immediately discontinued – and the proposed caffeine/ephedrine alkaloid restrictions should be withdrawn.

B. There Is No Scientific Evidence that Caffeine/Ephedrine Alkaloid Combinations Pose Health or Safety Concerns, and Scientific Evidence Suggests that These Combinations Are Safe.

FDA, in its initial Ephedra Proposal, proposed an outright prohibition on dietary supplements containing any and all levels of caffeine/ephedrine alkaloid combinations, and

³⁹ *Id.* at 17476 (emphasis added).

has refused to withdraw this prohibition in subsequent Federal Register notices. In other words, under the proposed rule, a dietary supplement containing 1 mg of ephedrine alkaloids and 1 mg of caffeine would be unlawful.

Notably, however, there is no science-based data in the administrative record that justifies this outright prohibition. In fact, this prohibition is particularly egregious because the administrative record fails even to address any level at which this combination allegedly poses health or safety concerns. This failure is not surprising because no such level has been established, and the Agency's own actions support this conclusion. The absence of scientific justification for FDA's outright prohibition of caffeine/ephedrine alkaloid combinations clearly renders FDA's proposed rule "arbitrary and capricious" in violation of the APA.

There is no scientific evidence that caffeine/ephedrine alkaloid combinations pose health or safety concerns. Notably, neither the Physician's Desk Reference ("PDR") for Herbal Medicines, nor the German Commission E Monographs Therapeutic Guide to Herbal Medicines, two well-respected authorities on herbal medicines, even list any contraindication for caffeine/ephedrine alkaloid combinations.⁴⁰ In fact, to the contrary, several scientific studies have concluded that caffeine/ephedrine alkaloid combinations are safe, including the following:

- One double-blind study, performed by a team of researchers in Denmark, compared the safety and efficacy of, *inter alia*, caffeine/ephedrine combinations (200 mg/ 20 mg) three times a day over a period of 15 weeks to a placebo, in a population of obese people who were 20% to 80% above their ideal body weight. Although 54% of the patients taking the combination complained of side effects, such as nervousness, the side effects were mild and "declined markedly during the first month of treatment."⁴¹
- As a continuation of a 24-week double-blind placebo controlled study, the same team of researchers in Denmark mentioned above, gave 127 patients caffeine/ephedrine combinations (200 mg/ 20 mg) three times a day for an additional 24-26 weeks, at which point the medication was stopped to evaluate withdrawal symptoms. The study concluded that "the ephedrine/caffeine combination is safe and effective in long-term treatment in improving and maintaining weight loss. The side-effects

⁴⁰ See PDR for Herbal Medicines (1st ed.), at 826-27; Blumenthal *et al.*, The Complete German Commission E Monographs: Therapeutic Guide to Herbal Medicine, at 125-26.

⁴¹ 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)(emphasis added).

are minor and transient and no clinically relevant withdrawal symptoms have been observed.⁴²

- In another study, performed by a team of researchers from Harvard Medical School, the safety and efficacy of an aspirin/caffeine/ephedrine combination (330 mg/150 mg/75-150 mg, respectively) in divided, pre-meal doses, was tested in 24 obese humans in a randomized, double-blind, placebo-controlled trial over a period of 8 weeks. Six subjects continued on the aspirin/caffeine/ephedrine mixture for 7 to 26 months. “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. [Aspirin/caffeine/ephedrine combinations] 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.”⁴³
- In another study conducted by the research team from Denmark, the safety and efficacy of the caffeine/ephedrine combination (200 mg/ 20 mg) consumed three times a day was tested in a randomized, double-blind, placebo controlled study against a dose of caffeine (200 mg) three times a day, and a dose of ephedrine (20 mg) three times a day, for 24 weeks. 180 obese people participated in this study. The study concluded that mean weight loss in the ephedrine/caffeine group was significantly greater than the weight loss in the group taking the placebo from week 8 to week 24, and that the weight loss in the groups taking only caffeine or ephedrine was similar to the weight loss in the group taking the placebo. Moreover, “[s]ide effects (tremor, insomnia, and dizziness) were transient and after 8 weeks of treatment they had reached placebo levels. Systolic and diastolic blood pressure fell similarly in all four groups.”⁴⁴

After carefully reviewing the leading studies on caffeine/ephedrine alkaloid combinations, including the Danish weight loss studies, Graham A. Patrick, Ph.D, R. Ph., a professor in the Department of Pharmacology and Toxicology at the Medical College of Virginia, concluded

⁴² 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)(emphasis added).

⁴³ P.A. Daly, *Ephedrine, Caffeine, and Aspirin: Safety and Efficacy for Treatment of Human Obesity*, 17 International Journal of Obesity and Related Metabolic Disorders (Supplement 1) S73 (1993)(emphasis added).

⁴⁴ 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)(emphasis added). See also A. Malchow-Miller, *Ephedrine as an Anorectic: 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”).

that “[t]here is insufficient data to determine that the co-administration of caffeine with ephedrine increases the likelihood of serious adverse effects,” for the following reasons:

- In clinical studies of caffeine/ephedrine combinations for weight loss, the combination did not produce significantly more frequent, nor more severe side effects than ephedrine alone.⁴⁵
- In the studies where more total side effects were reported by patients receiving caffeine, ephedrine, or a caffeine/ephedrine combination, than the patients receiving the placebo, the “difference between those groups and the placebo was only significant at the first 4-week checkpoint. . . . In fact, the tachycardic effect (sense of racing heart) from ephedrine was actually counteracted by combination with caffeine.”⁴⁶
- Ephedra product users are likely to consume larger quantities of caffeine from their regular diet than the amount included in combination products.⁴⁷

The studies listed above, as well as Dr. Graham’s review of the studies, counter FDA’s outright prohibition on caffeine/ephedrine alkaloid combinations.

In the instant case, the absence of scientific support demonstrating a safety issue associated with low level combinations of ephedrine alkaloids and caffeine renders a complete ban on such combinations “arbitrary and capricious” in violation of the APA. Moreover, the absence of data supporting any level at which such combinations pose safety concerns would also render any restrictions on caffeine/ephedrine alkaloid combinations unlawful.

C. FDA’s Own Actions Support the Conclusion that Caffeine/Ephedrine Alkaloid Combinations, at All Levels, Pose No Health or Safety Concerns.

Over the years, FDA has had numerous opportunities to evaluate the safety of caffeine in combination with ephedrine alkaloids under the Agency’s regulatory authority over conventional food products and drugs. FDA, however, has never identified any safety concerns associated with the combination.

For example, FDA has never required OTC drug products that contain ephedrine alkaloids to bear warning labels advising against ingestion along with foods that contain caffeine (such as coffee and tea). Moreover, FDA has never required caffeine-containing food products

⁴⁵ See Graham A. Patrick, Ph.D, R. Ph., *Preliminary Commentary on Food and Drug Administration Proposed Rule on Limitations on Dietary Supplements Containing Ephedrine Alkaloids*, at 7.

⁴⁶ *Id.*

⁴⁷ *See id.*

(such as coffee and tea) to bear warning labels advising against ingestion of drug products containing ephedrine alkaloids. Rather, the only concern identified by the Agency regarding caffeine/ephedrine alkaloid combinations has been the potential misuse of such combinations. Such misuse concerns are entirely distinguishable from safety concerns associated with normal conditions of use.

Specifically, 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/phenylpropanolamine combinations, which are marketed as illicit street drug alternatives.⁴⁸ FDA issued these Advisory Opinions solely due to concerns regarding the misuse and abuse of such products (*i.e.* to get high), *not* the safety of those products under normal conditions of use.⁴⁹

In its Advisory Opinions, FDA recognized that the actual 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].”⁵⁰ According to the FDA, because these products are marketed and promoted as illicit street drug alternatives, they are misused and abused.⁵¹ Notably, FDA, in its Advisory Opinions, does not claim that merely ingesting OTC drug products that contain caffeine/ephedrine or caffeine/phenylpropanolamine causes health problems. Nor 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 entirely distinguishable from safety concerns associated with normal use consistent with use recommendations.

Accordingly, the ephedrine OTC drug products can readily be distinguished from dietary supplements containing ephedrine alkaloids because legitimate dietary supplements are not marketed as illicit street drug alternatives. Misuse concerns, therefore, do not provide the Agency with a legitimate reason to ban dietary supplements containing caffeine/ephedrine alkaloid combinations. In fact, banning dietary supplements containing caffeine/ephedrine alkaloids in the name of preventing misuse would be unlawful as, according to DSHEA, dietary supplement safety must be evaluated in connection with the “conditions of use recommended or suggested in labeling.”⁵²

⁴⁸ See 49 Fed. Reg. 26814 (June 29, 1984); 48 Fed. Reg. 52513 (Nov. 18, 1983).

⁴⁹ See 48 Fed. Reg. at 52513 (“The intended effect of this action is to eliminate abuse and misuse of these products”).

⁵⁰ *Id.*

⁵¹ *Id.*

⁵² 21 U.S.C.A. § 342(f)(1) (West 2000).

Moreover, to the extent FDA is concerned about misuse, the Agency has already addressed such concerns in a guidance document entitled “Guidance for Industry: Street Drug Alternatives,” which was issued on April 3, 2000.⁵³ In this guidance document, FDA indicated that products intended for use for recreational purposes to affect psychological states (e.g. to get high, promote euphoria, or induce hallucinations) are unapproved new drugs subject to FDA enforcement.⁵⁴ In the Agency’s notice of availability for this guidance document, FDA specifically stated:

These street drug alternatives are generally labeled as containing botanicals, and some are also labeled as containing other ingredients, such as vitamins, minerals, or amino acids. They are marketed under a variety of brand names with claims implying that these products mimic the effects of controlled substances. These products are intended to be used for recreational purposes to effect psychological states. This guidance is intended to inform industry and the public that FDA considers any product that is promoted as a street drug alternative to be an unapproved new drug and a misbranded drug in violation of [the FFDCA].⁵⁵

As demonstrated by this policy, the Agency has ample authority to address misuse concerns (i.e. use to “get high”) associated with caffeine/ephedrine alkaloid combination products marketed for inappropriate reasons. However, such concerns are appropriately addressed by guidance documents specifically targeting misuse, not a categorical ban on caffeine/ephedrine alkaloid combinations in lawful dietary supplement products. There is no evidence to suggest that such combinations are not safe when included in legitimate dietary supplement products that are not promoted as “street drugs” and when ingested in accordance with recommendations for use.

⁵³ See *Guidance for Industry: Street Drug Alternatives*, FDA (Mar. 2000).

⁵⁴ See *id.*

⁵⁵ 65 Fed. Reg. 17512 (Apr. 3, 2000) (summarizing key statements in *Guidance for Industry: Street Drug Alternatives*, FDA (Mar. 2000)).

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

The 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.”⁵⁶ To assess whether an agency has overstepped its bounds, a court must begin by inquiring whether Congress intended to give an agency jurisdiction over a particular matter.⁵⁷ “If the intent is clear, that is the end of the matter; for the court, as well as the agency, must give effect to the unambiguously expressed intent of Congress.”⁵⁸

Congressional intent is particularly important in the instant case because FDA is attempting to expand the scope of its jurisdiction from regulating “adulterated” dietary supplements on a product-by-product basis to regulating an entire class of allegedly “adulterated” dietary supplements via notice and comment rulemaking procedures.

However, the plain language of the FFDCA,⁵⁹ as amended by DSHEA⁶⁰ is clear – the FFDCA authorizes FDA to regulate “adulterated” dietary supplements only on a product-by-product basis, not on a class basis. The plain language of Section 402(f)(1) of the FFDCA,⁶¹ as amended by the Dietary Supplement Health and Education Act of 1994 (“DSHEA”)⁶² authorizes FDA to regulate “adulterated” dietary supplements on a product-by-product basis only.⁶³ The proposed rule exceeds this authority because it attempts to

⁵⁶ 5 U.S.C.A. § 706(2)(C) (West 2000);⁵⁶ *Bowen v. Georgetown Univ. Hosp.*, 488 U.S. 204, 208 (1988); see *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”).

⁵⁷ See *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).

⁵⁸ See *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”) (emphasis added).

⁵⁹ 21 U.S.C.A. §§ 321-97 (West 2000).

⁶⁰ Pub. L. No. 103-417, 108 Stat. 4325 (1994) (codified in scattered sections of Title 21 of the United States Code, amending portions of the FFDCA).

⁶¹ 21 U.S.C.A. §§ 321-97 (West 2000).

⁶² Pub. L. No. 103-417, 108 Stat. 4325 (1994) (codified in scattered sections of Title 21 of the United States Code, amending portions of the FFDCA).

⁶³ See 21 U.S.C.A. § 342(f)(1) (West 2000); see also *FDA Statement on Street Drugs Containing Botanical Ephedrine*, FDA Press Release, Apr. 10, 1996 (“[U]nder 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”).

regulate all dietary supplements containing ephedrine alkaloids on a class basis, rather than product-by-product basis.

V. Conclusion

For the above reasons, we respectfully request that the Agency terminate the entire rulemaking process associated with dietary supplements that contain ephedrine alkaloids, and instead adopt the industry-proposed CPG previously provided to the Agency (See Attachment A) that establishes reasonable standards for the dietary supplement industry. Such standards should not, however, include restrictions on caffeine/ephedrine alkaloid combinations due to the absence of any safety issues associated with such combinations.

Respectfully submitted,



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Attachment A

DRAFT CFSAN COMPLIANCE POLICY GUIDE
FOR DIETARY SUPPLEMENT PRODUCTS CONTAINING
EPHEDRINE ALKALOIDS

CPG 530.____ DIETARY SUPPLEMENT PRODUCTS CONTAINING
EPHEDRINE ALKALOIDS

REGULATORY ACTION GUIDANCE

The following represents the criteria for recommending legal action to
CFSAN/Office of Field Programs/Division of Enforcement:

1. If the product contains on a per serving basis more than 25mg of ephedrine alkaloids (the total of ephedrine, pseudoephedrine, norpseudoephedrine, norephedrine, methyl ephedrine, methyl pseudoephedrine and related alkaloids).
2. If the product label does not list the amount of ephedrine alkaloids per serving.
3. If the recommended daily intake specified on the product label exceeds 100mg of ephedrine alkaloids per day.
4. If the product contains xanthine alkaloids (collectively identified as caffeine) and the product label does not list the amount of caffeine per serving.
5. If the product label does not bear an adequate warning statement, which shall at a minimum include the following language, or comparable language:

Not for use by anyone under the age of 18. Do not use this product if you are pregnant or nursing. Consult a health care professional before using this product if you have heart disease, thyroid disease, diabetes, high blood pressure, psychiatric condition, difficulty in urinating due to prostate enlargement, or seizure disorder, if you are using a monoamine oxidase inhibitor (MAOI) or any other prescription drug, or if you are using an over-the-counter drug containing ephedrine, pseudoephedrine or phenylpropanolamine (ingredients found in certain allergy, asthma, cough/cold and weight control products).

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

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

6. If any claims are made that the product may be useful to achieve an altered state of consciousness, euphoria, or as a “legal” alternative for an illicit drug.
7. If the product is marketed or offered for sale to minors.