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April 7, 2003

BY ELECTRONIC MAIL/CONFIRMATION
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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket 95N-0304
Dietary Supplements Containing Ephedrine Alkaloids[1]

Dear Sir or Madam:

The Ephedra Education Council ("EEC") submits these comments on the Food and Drug Administration's ("FDA's") proposed rule on dietary supplements containing

[1] We have been informed by officials at FDA that in reopening the ephedra-related docket, the agency will include within Docket 95N-0304 all ephedra-related information provided to the agency since the initiation of its ephedra review. Accordingly, it is our clear understanding that the official "administrative record" will include all materials and information provided to FDA in all of the ephedra-related administrative dockets – including, but not limited to, Dockets 95N-0304 (current proceeding), 00N-1200 (adverse event reports associated with the use of dietary supplements containing ephedrine alkaloids), and 01P-0396 (request that FDA ban the production and sale of all ephedra products). We officially incorporate by reference into this submission all of the materials and information contained in the above mentioned dockets.

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ephedrine alkaloids ("ephedra supplements").[2] FDA has requested comments on a proposed warning label for ephedra supplements, and on whether these supplements in general, despite a very broad range of different formulations and serving amounts, represent a "significant or unreasonable risk of illness or injury under conditions of use recommended or suggested in labeling, or, if no conditions of use are suggested or recommended in the labeling, under ordinary conditions of use."[3] FDA has also requested comment on "what additional legislative authorities, if any, would be necessary or appropriate to enable FDA to address this issue most effectively."[4]

The EEC lauds this initiative by FDA to finally issue a uniform national warning label for all ephedra products which preempts various state warnings that have been implemented during the long period of FDA delay on this matter. A national warning label has been requested on at least three separate occasions by industry. It was first requested in comments to FDA's proposed rule in 1997, then during a May 1999 meeting with the head of Center for Food Safety and Applied Nutrition ("CFSAN"), and again in October 2000 in a joint petition by the dietary supplement trade associations, to which FDA never substantively responded.

However, the principal display panel warning that FDA has proposed goes far beyond what is justified by the science relating to the safety and benefits of ephedra, and misleads consumers to believe that ephedra has caused heart attacks, strokes, seizures and deaths, when the RAND Report[5] concludes just the opposite. The proposed warning states that reports of serious adverse events have been submitted to FDA. While there have been some rare occurrences of these events, FDA has never established a causal connection between these rare occurrences and the consumption of ephedra products. Moreover, since there is no uniform pattern with respect to these events, it is factually incorrect, or at the very least misleading, to imply that ephedra products caused these

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[2] In using the term "ephedra supplements," we are referring to the herb ephedra, or extracts thereof. This term is not intended to encompass synthetic ephedrine.

[3] 68 Fed. Reg. 10,417, 10,419 (Mar. 5, 2003) (reopening of comment period for initial proposal on ephedrine regulation); see also 62 Fed. Reg. 30,678 (June 4, 1997) (proposed rule) ("Ephedrine Proposal").

[4] 68 Fed. Reg. at 10,420.

[5] Paul Shekelle, et al., Ephedra and Ephedrine For Weight Loss and Athletic Performance Enhancement: Clinical Efficacy and Side Effects, AHRQ Pub. No. 03-EO22 (Feb. 2003) ("RAND Report").

events or caused them to a degree which correlates with any measurable risk at all. For FDA to state that such reports have been received, without a qualifying statement that there is no established causal link and that reports of serious adverse events are extremely rare, merely serves to confuse and mislead consumers. A strong, comprehensive warning is needed, but the required warning should provide consumers with accurate information to facilitate informed choices, rather than blatantly mislead them – as does the current proposed warning.

Furthermore, it is premature for FDA to request comments on whether ephedra supplements present a "significant or unreasonable risk of illness or injury." This standard for adulteration was established for dietary supplements in 1994 by the Dietary Supplement Health and Education Act ("DSHEA") but has never been defined by FDA. FDA's uncertainty as to the meaning of this standard is reflected in the "White Paper" issued on the same day as this proposed rulemaking, titled "Evidence on the Safety and Effectiveness of Ephedra: Implications for Regulation."[6] The White Paper for the first time begins to ask questions about the meaning of the adulteration standard for dietary supplements. FDA must first conduct a rulemaking, or at a minimum develop guidance, on this new standard prior to seeking comment on and making a determination of the status of ephedra supplements under this standard. That FDA has failed to focus on this threshold inquiry until now is emblematic of the agency's failure and reluctance to implement DSHEA.

However FDA defines the standard for the "significant or unreasonable risk" that would render a dietary supplement adulterated under DSHEA, there is no question that ephedra supplements that meet current industry standards are safe and provide significant public health benefits for consumers who need to lose weight. Therefore, these products do not present a "significant or unreasonable risk of illness or injury under conditions of use recommended or suggested in labeling, or . . . under ordinary conditions of use." The two most recent and comprehensive scientific reviews of ephedra, the RAND Report and the Cantox Report,[7] establish three things: (1) ephedra supplements provide a significant weight loss benefit;[8] (2) a risk assessment of ephedra and caffeine based on human

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[6] FDA, Evidence On the Safety and Effectiveness of Ephedra: Implications for Regulation (Feb. 28, 2003) ("White Paper").

[7] Cantox Health Sciences International, Safety Assessment and Determination of Tolerable Upper Limits for Ephedra (Dec. 19, 2000), (Prepared for the Council for Responsible Nutrition) ("Cantox Report").

[8] As will be shown below, the available data that support weight loss benefits for

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clinical data, and supported by and consistent with extensive animal toxicological data, shows that ephedra products are safe when properly labeled and formulated; and (3) adverse event reports ("AERs") are not useful for assessing safety, and do not establish that ephedra has caused serious adverse events.

Finally, there is absolutely no basis for concluding that FDA has a need for additional legislative authority to address issues relating to ephedra or any other dietary supplement issues. At least one FDA Commissioner since the passage of DSHEA has consistently stated, and has testified before Congress, that DSHEA provides ample authority to regulate dietary supplements. The current misconception by the press and public that ephedra might cause serious adverse events, and that FDA can do nothing about it, is a problem that FDA itself created through press releases and its 1997 proposed rule. In these documents FDA stated repeatedly that it had received reports of deaths and other serious adverse events "associated with" ephedra, with the clear implication that FDA had determined there was a causal link.[9] In fact, FDA later admitted to the General Accounting Office ("GAO") that FDA was not claiming that there was any causal link to ephedra, and that FDA had not even reviewed the reports to assess whether there was even a remote possibility of causation. As the AERs themselves reveal, most of them are useless in determining causation because they are so incomplete, and those that are complete are inconclusive. Almost six years after FDA initiated the public perception that ephedra was likely causing serious adverse events, including deaths, we now have independent confirmation from RAND that these reports do not establish a cause-and-effect relationship between ephedra and the events that were the subjects of the AERs at issue.[10] Further, FDA's "attempt" to regulate ephedra through its 1997 proposed rule was so woefully deficient on science that it led to an extensive GAO audit and report that, in

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ephedra are essentially the same as the data that FDA has used to approve weight loss drugs that are currently on the market, in terms of the length of the studies involved. Therefore, there is no question that, under current standards for evaluation of such products, ephedra supplements provide significant public health benefits.

9 See, e.g., Press Release, FDA, Department of Health and Human Services ("HHS"), FDA Warns Consumers Against Nature's Nutrition For Formula One (Feb. 28, 1995) (Attachment A).

10 Letter from Tommy G. Thompson, Secretary, HHS, to Sidney Wolfe, M.D., Public Citizen's Health Research Group, at 2 (June 14, 2002).

turn, caused FDA to take the unprecedented step of withdrawing most of the proposal for lack of a sufficient scientific basis.

The scientific data should not be eclipsed by the storm of controversy generated by the media and the agency itself. The safety and benefits of ephedra products can be assured with proper implementation of current laws, which allow FDA to require that the products be appropriately labeled, formulated, and manufactured with quality controls. DSHEA has aided, not hampered, FDA efforts to remove unsafe dietary supplements from the market when there is a scientific basis to do so. It is untrue that the law permits the marketing of dietary supplements that lack scientific support for safety and claims for benefits.

Thus, instead of asking for more authority, FDA should begin to implement the considerable legislative authority it currently has under DSHEA. Further, FDA should issue a science-based warning as soon as possible, and industry and government should collaborate in completing the science-based review of the safety and benefits of ephedra that RAND has recommended.

The basis for these comments is discussed in further detail below.

I. Background

FDA's proposal is actually a reopening of the comment period for FDA's 1997 proposed rule entitled "Dietary Supplements Containing Ephedrine Alkaloids," which proposed, in pertinent part, that ephedra supplements bear a warning statement and that they be restricted in their potency and composition, as well as in their labeling claims and direction for use.[11] FDA proposed the rule "in response to serious illnesses and injuries, including multiple deaths, associated with the use of dietary supplement products that contain ephedrine alkaloids and the agency's investigations and analyses of these illnesses and injuries."[12]

On April 3, 2000, parts of this original proposal were withdrawn because "of concerns regarding the agency's basis for proposing a certain dietary ingredient level and a duration of use limit for" ephedra supplements.[13] The concerns stemmed from the GAO's examination of the scientific bases for the 1997 proposal, which found, among

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[11] Ephedrine Proposal, 62 Fed. Reg. 30,678.

[12] Id.

[13] 65 Fed. Reg. 17,474 (Apr. 3, 2000) (partial withdrawal of Ephedrine Proposal).

other things, that FDA needed more evidence than AERs to support the proposed dosing level and duration of use limit.[14] GAO stated that the AERs were of questionable quality, and "FDA did not establish a causal link between the ingestion of ephedrine alkaloids and the occurrence of particular adverse events."[15]

Almost six years have passed since the original proposal, and FDA has reopened the comment period to receive additional comment and to propose a warning label. As discussed below, the science today provides stronger support for continued marketing of ephedra for weight loss with appropriate warnings.

II. No Additional Legislative Authority Is Needed To Regulate Ephedra Supplements

FDA has raised the question of whether the agency needs additional legislative authority to regulate ephedra supplements. The answer is no. This question misses the mark. Rather, as discussed below, FDA should focus its attention not on the need for additional authority, but on duly and lawfully implementing the authority it already has with respect to supplements.

Since the inception of DSHEA, industry and FDA have been in agreement that ephedra products needed standards to require serving limits and label warnings. The record establishes that FDA has completely ignored industry's attempts to work with the agency and has mishandled its attempts to regulate these products. FDA needs to act in a scientifically responsible manner and regulate ephedra and all supplements based on science, rather than trying to fit the science to the agency's preconceived notion that ephedra is unsafe.

- First, FDA issued a proposed rule in 1997 that banned marketing for weight loss and limited servings to arbitrarily low levels. The proposal was a monumental waste of government and industry resources. After a year-long audit of FDA's proposal, the GAO concluded that it lacked a scientific basis, and recommended that FDA not implement the proposal unless additional science could be found to support it.

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[14] Id. at 17,475; GAO, Dietary Supplements: Uncertainties in Analyses Underlying FDA's Proposed Rule on Ephedrine Alkaloids, at 24 (July 1999) ("GAO Report").

[15] Id.

- In response, FDA collected additional AERs and provided them to outside experts for analysis, while refusing to respond to repeated industry Freedom of Information Act ("FOIA") requests for the same documents for a period of almost two years.[16] In April of 2000, FDA simultaneously withdrew the portions of the proposed rule criticized by GAO, released its outside expert reviews of the new AERs, and declared ephedra a serious health risk based on information that the agency had refused to provide to industry, in violation of the Freedom of Information Act.

- The Department of Health and Human Services (HHS) convened a Public Meeting in August 2000 before a large panel of experts to review FDA's assessment of ephedra as a serious public health risk. At this meeting, clinical researchers established that FDA had mischaracterized published clinical data to support the agency's view that ephedra was not safe.[17] HHS issued a report in September of 2000 that expressed concerns about ephedra, but did not agree with FDA that ephedra represented a serious public health risk. Instead, HHS recommended that industry and government work together to pursue research to address questions relating to ephedra, starting with a comprehensive review of current data to identify any research gaps.[18] FDA has never followed HHS's recommendation to work with industry despite industry's repeated offers to do so.

- FDA has failed to respond to overtures taken by industry to address a number of issues, including the October 2000 citizen petition submitted by industry trade groups requesting that the American Herbal Products Association ("AHPA") trade recommendation's formulation, labeling, and marketing requirements be adopted for all ephedra supplements. FDA sent a response stating that the issues were "too complex," but never responded substantively to the petition.[19]

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16 Id.; see, e.g., FOIA Request from Josh Berlin, former legal assistant, Hyman, Phelps & McNamara, P.C., to FDA (June 17, 1998) (Attachment B).

17 See Office on Women's Health, HHS, Transcript of Public Meeting on the Safety of Dietary Supplements Containing Ephedrine Alkaloids (Aug. 8-9, 2000).

18 See Office on Women's Health, HHS, Meeting Summary of Public Meeting on the Safety of Dietary Supplements Containing Ephedrine Alkaloids (Aug. 8-9, 2000).

19 On October 25, 2000, a group of industry trade associations submitted a petition to

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- Based on HHS's recommendations and on funding from Congress, the RAND study was funded, and the recent RAND Report published, confirming the weight loss benefits of ephedra, the lack of a single serious adverse event in any clinical studies, and the inability of using AERs for assessing ephedra's safety. RAND has responsibly recommended further scientific studies to answer remaining questions, a concept that industry embraces. This recommendation – in light of the weight loss benefits of ephedra and the absence of a real safety issue – weighs in favor of a finding that ephedra supplements do not pose a significant or unreasonable risk.

It is apparent that this is not a record of which FDA should be proud. More to the point, it is certainly not a record that supports the notion that additional legislative and regulatory authority is the solution.

Indeed, one FDA Commissioner has expressly recognized that DSHEA grants the agency sufficient authority to regulate supplements, including the power to remove them from the marketplace if circumstances warrant. In 1999, in a statement before the House Committee on Government Reform on FDA's implementation of DSHEA, Commissioner Jane Henney acknowledged the authority granted to FDA under DSHEA "to remove from the market products that pose a 'significant or unreasonable' risk to consumers or that are otherwise adulterated and to require that labeling for dietary supplements be accurate."[20] Commissioner Henney concluded her remarks by stating that, "DSHEA provides FDA with the necessary legal authority to protect the public health."[21]

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FDA requesting that the agency adopt labeling and marketing requirements for ephedra supplements. See Citizen Petition submitted by American Herbal Products Association, The Consumer Healthcare Products Association, The National Nutritional Foods Association, and The Utah Natural Products Alliance (Oct. 25, 2000) ("Industry Petition") (Attachment C).

[20] Jane E. Henney, M.D., Statement on FDA Regulations on Dietary Supplements Address Before the House Committee on Government Reform, at Sec. III (Mar. 25, 1999).

[21] Id.; see also Stephen H. McNamara, et al., DSHEA Provisions Confine FDA's Authority to Issue Regulations That Concern Allegedly Adulterated Dietary Supplements, 54 Food & Drug L. J. 595 (1999) (concluding that FDA has ample authority to regulate ephedra and all other dietary supplements).

The EEC therefore recommends that FDA continue its process of implementing DSHEA by focusing on the authority it was given by DSHEA to regulate supplements. A prudent starting point, as discussed below, would be the formulation of a definition of "significant or unreasonable risk."

III. FDA Must First Define the Significant or Unreasonable Risk Standard

FDA has requested comment on "whether in light of current information FDA should determine that dietary supplements containing ephedrine alkaloids present a 'significant or unreasonable risk of illness or injury under conditions of use recommended or suggested in labeling, or if no conditions of use are suggested or recommended in the labeling, under ordinary conditions of use.'"[22] However, the term "significant or unreasonable risk of illness or injury" is undefined in DSHEA, and FDA has failed to establish working definitions of what constitutes a "significant risk" or "unreasonable risk." A threshold step in determining whether any dietary supplement product meets this standard should be a rulemaking to establish a definition for the standard, or, at a minimum, the issuance of guidance on this important subject for public comment. It is therefore premature for the agency to attempt to engage in a determination of whether ephedra supplements present a "significant risk" or "unreasonable risk" to health, when no working definition exists for these terms.

IV. Ephedra Supplements Do Not Present a "Significant or Unreasonable Risk of Illness or Injury Under Conditions of Use Recommended or Suggested in Labeling, or . . . Under Ordinary Conditions of Use"

Although significant new evidence on the safety of ephedra supplements has emerged in the last six years, none of it demonstrates that ephedra supplements pose a "significant or unreasonable risk of illness or injury under conditions of use recommended . . . or . . . under ordinary conditions of use." As established below, the studies clearly show that ephedra supplements are safe under any standard and provide important public health benefits. Regardless of how FDA defines the standard of "significant or unreasonable risk," the science overwhelmingly supports the safety and benefits of ephedra when properly labeled, formulated and consumed.

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[22] 68 Fed. Reg. at 10,419 (citing 21 U.S.C. § 342(f)(1)).

A. A Finding that All Ephedra Products Represent a "Significant or Unreasonable Risk" Would Necessarily Be Arbitrary Given the Wide Variety of Products that Any Such Finding Might Include

DSHEA does not authorize a finding of "adulteration" of a supplement on the basis that it poses an "unreasonable risk of illness or injury." Rather, risks must be assessed under the "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."[23]

Thus, if the labeling of a dietary supplement recommends or suggests particular conditions of use, any determination about whether the product presents a "significant or unreasonable risk of illness or injury" should be made based upon use of the product under the conditions that are recommended or suggested. For example, if a product is explicit in its labeling that it should be taken only once a day, or that it should not be taken by persons who are also taking a prescription drug, or by pregnant women, or by persons under the age of 18, or if any other condition of use is specified in the labeling, any assessment about whether the product presents a "significant or unreasonable risk of illness or injury" should not include any consideration of whether the product might present such risk to persons who consume more than the recommended daily amount or who otherwise consume the product in violation of the directions for use, warnings against unrecommended use, or other conditions of use specified in the labeling. All responsible manufacturers of ephedra supplements warn against use by or sales to minors, and also include comprehensive warnings of contraindications for use of ephedra products.[24]

Further, FDA must take into consideration differences in dosing and formulation of the products involved. FDA has not begun to explain how it intends to determine whether ephedra supplements present a "significant or unreasonable risk of illness or injury under conditions of use . . . suggested or recommended in the labeling . . . or, under ordinary conditions of use" given that there are numerous ephedra supplements on the market, ranging from the whole herb ephedra to extracts of ephedra, and presenting a range of ephedrine alkaloid content.[25] Under these circumstances, any finding that all

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[23] 21 U.S.C. § 342(f)(1)(A) (emphasis added).

[24] Industry Petition at 2-3.

[25] 68 Fed. Reg. at 10,419.

dietary supplements containing ephedra are adulterated under applicable standards would be arbitrary and capricious and in violation of law.

B. The Available Science Supports the Safety and Benefits of Ephedra When Properly Labeled and Consumed

Although FDA has not formally defined the term "significant or unreasonable risk," it is clear at this juncture that, however it is ultimately defined, the available literature and clinical trial results do not support a finding that ephedra supplements meet such a standard.

- Ephedra has significant benefits that significantly outweigh any risks. In the opinion of Dr. Frank Greenway, a leading bariatric researcher from the Pennington Biomedical Research Center, clinical data establish that ephedra has clear and important health benefits for overweight Americans, and that the benefits far outweigh any risks.[26] Dr. Greenway's conclusions are supported by the RAND Report, as well as by new clinical data that RAND did not consider.

- Ephedra is safe when labeled and formulated according to industry standards. This fact is established by the only comprehensive risk assessment that has ever been conducted on ephedra, performed by one of the leading toxicology firms, Cantox Health Sciences International, which is routinely consulted by FDA, the National Academy of Sciences and others for its expertise in safety issues. The Cantox risk assessment has already been submitted to the ephedra docket, and Cantox has submitted additional comments in response to the reopening of the ephedra docket.[27] The RAND Report, while not a formal risk assessment, is consistent with the Cantox Report in its findings of no reports of any serious adverse event reports from any clinical studies.

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[26] See Frank Greenway, M.D., Comments on Proposed Rule For Dietary Supplements Containing Ephedrine Alkaloids (March 21, 2003) ("Greenway Comments") (Attachment D).

[27] See Cantox Health Sciences International, Comments on Proposed Rule for Dietary Supplements Containing Ephedrine Alkaloids; Food and Drug Administration; HHS [Docket No. 95N-0304], (April 3, 2003) ("Cantox Comments") (Attachment E).

- The RAND Report confirms that adverse event reports do not establish a cause-and-effect relationship between ephedra and rare reports of serious events, including heart attack, stroke, seizure and death.[28]

- The RAND Report recommends further research to provide additional confirmation of benefits and to test the "hypothesis" that ephedra might cause rare but serious adverse events. This conclusion confirms that, in RAND's view, an FDA determination that ephedra products present "a significant or unreasonable risk" and should therefore be removed from the market is not supportable.[29]

1. RAND Report Supports the Safety and Benefits of Ephedra

The authors of the RAND report, which was commissioned, in part, by the National Institute of Health's Office of Dietary Supplements, assessed both the safety and the benefits of ephedra. The RAND Report concluded that "[s]hort-term use of ephedrine, ephedrine plus caffeine, or dietary supplements containing ephedra with or without herbs containing caffeine is associated with a statistically significant increase in short-term weight loss (compared to placebo).[30] The numerous recent studies on ephedra, including a year-long study not considered by RAND, are reviewed in an attached comment from Dr. Frank Greenway.[31] According to Dr. Greenway, ephedra and caffeine satisfy FDA efficacy criteria for approving drugs for the treatment of obesity:

> [E]phedrine/caffeine and ephedra/caffeine appear to be at least as efficacious for weight loss as the presently available prescription drugs approved for that purpose. The obesity drugs available by prescription were approved based on a risk benefit assessment. Therefore, to the extent that approved obesity prescription medications are effective for weight loss and the treatment of obesity, ephedrine or ephedra with caffeine are as well. Thus, the statement quoted from the Rand Report

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28 RAND Report at 203.

29 Id. at 205.

30 Id. at vi; see also id. at 201.

31 See Greenway Comments.

> in the first paragraph should not be interpreted as a lack of efficacy for ephedra or ephedrine with caffeine to help consumers lose weight.[32]

The significant health benefits of these products, according to experts in weight loss, are already established by clinical research.

The RAND Report also "assessed [the] safety of [herbal ephedra-containing dietary supplements] through review of adverse events reported in clinical trials, published case reports of adverse events, reports on file with [FDA], and a file of reports kept by a manufacturer of ephedra products."[33] The authors concluded that "[t]he majority of case reports are insufficiently documented to make an informed judgment about a relationship between the use of ephedrine or ephedra-containing dietary supplements and the adverse event in question."[34] They stated that the reports warrant a "hypothesis-testing study, such as a case-control study, to support or refute the hypothesis that consumption of ephedra or ephedrine may be causally related to these serious adverse events."[35] Thus, the RAND Report confirmed what has been stated to FDA all along – that AERs cannot be used to show causality between the consumption of ephedra supplements and serious adverse events.

That FDA has heard this message and understands it was made clear in HHS's June 14, 2002 letter to Sidney Wolfe concerning ephedra products:

> [T]he FDA has advised . . . that the types of observed outcomes reported in relationship to the ingestion of ephedrine alkaloids are not uncommon in the general population and therefore the reports alone do not provide a scientific basis for assessing the safety of ephedrine alkaloids or establish a link between the reported adverse events and the ingestion of ephedrine alkaloids.[36]

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32 Id. at 2-3.

33 RAND Report at v.

34 Id. at vi; see also id. at 199.

35 Id. at vii (emphasis added).

36 Letter from Thompson to Wolfe at 2 (June 14, 2002).

As far as side effects (and not serious adverse events) from ephedra supplement consumption, the RAND Report noted that the clinical trials they reviewed provided "sufficient evidence" "to conclude that the use of [ephedra supplements] is associated with two to three times the risk of nausea, vomiting, psychiatric symptoms such as anxiety and change in mood, autonomic hyperactivity, and palpitations."[37] However, these side effects, when evaluated in a risk/benefit analysis, are few and minor in comparison to the public health benefit that results from ephedra supplement consumption.[38]

It is also important to note that not a single serious adverse event has ever been reported in any of the double blind clinical studies that RAND has reviewed. Were it accurate that ephedra posed a significant or unreasonable risk, it would be incomprehensible that not one serious adverse event has been reported.

Finally, the RAND Report's recommendation that additional research on benefits and safety, and not further review of AERs, be conducted to address any remaining questions, establishes unequivocally that the RAND Report provides no scientific basis for a determination that ephedra supplements are adulterated under the "significant or unreasonable risk" standard.[39] The RAND Report was designed to provide a comprehensive review of the science. FDA should follow the path that RAND has set, and issue a final rule for a warning label and support the additional research that RAND recommended.

1. The Cantox Report Establishes the Safety of Ephedra Products When Labeled According to Industry Standards

The Cantox Report, already part of FDA's ephedra docket, conducted a risk assessment of ephedra products, with or without caffeine, when labeled according to current industry standards as exemplified by the AHPA Ephedra Trade Recommendation. Cantox has submitted separate comments[40] that establish the continued validity of the

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37 RAND Report at vi, 202-03.

38 See Greenway Comments.

39 RAND Report at 205.

40 See Cantox Comments.

Cantox risk assessment and its consistency with the findings of RAND.[41] According to Cantox:

> Based principally on the rare but well-publicized incidents of adverse events that have been associated with ephedra, the FDA proposes reconsideration of its possible use in the United States. Clearly from a scientific perspective dose levels in the range of 90 mg/d (30 mg 3 times/day) are safe for human consumption, and these amounts do not present "a significant or unreasonable level of risk of disease or injury" when used according to label directions, however that safety standard is defined. As the law appropriately suggests, the FDA cannot assume responsibility for protecting the public from themselves, if they choose to use this or any other product at higher than recommended levels or otherwise misuse properly labeled products. In this regard, the proposed warning should make reference to dose. The overwhelming majority of ephedra users in the United States are responsible consumers who should continue to have access to this and other products that are produced, labeled, and sold by responsible manufacturers.[42]

2. EEC Expert Committee Consensus Findings

On October 2, 2002, the Expert Panel of the EEC submitted comments to FDA on the safety of dietary supplements containing ephedrine alkaloids and on the AERs and health assessments released by FDA on April 3, 2000.[43] The Expert Panel's comments were obtained from an analysis of the published literature on the safety and usefulness of ephedra supplements; an analysis of FDA's literature review of ephedra; an analysis of published data on the incidence rates of seizures, strokes, and myocardial infarctions in the general population compared to estimates of incidence rates in consumers of ephedra supplement; a review of 276 AERs reported to FDA; and an analysis of the abuse

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41 Id. at 1, 4.

42 Id. at 7.

43 EEC Expert Panel's Comments, 1-32 (Sept. 29, 2000) (Attachment F). The remainder of the Expert Panel's Comments, which were submitted to Docket No. 00N-1200, are hereby incorporated by reference.

potential of ephedrine alkaloids. The findings of the Expert Panel are entirely consistent with the conclusions of RAND.

Regarding the safety of ephedra supplements, the Expert Panel concluded that the available information does not demonstrate an association between the use of dietary supplements containing ephedrine alkaloids and serious adverse events when used according to the AHPA Trade Recommendation. The Expert Panel also concluded that given the absence of data demonstrating an association between ephedra supplements and serious adverse events, the presence or absence of a "susceptible population" cannot be determined; however, severe overdosing can lead to serious adverse events, and minor and/or very rare idiosyncratic reactions may occur (e.g., skin rashes, allergic reactions) with use at recommended serving sizes, as they can with any ingested food.[44] The panel stated that the pathology data available do not show any pattern consistent with ephedrine alkaloid-containing dietary supplements as a cause of death.[45] Finally, consistent with RAND, the EEC Expert Panel recommended further research to resolve questions arising from widespread publicity of reports of rare, inconclusive but serious adverse events.

3. Other Evidence of Safety

Numerous other clinical studies that do not appear to have been reviewed by the RAND authors support the safety of ephedra supplements. These studies provide further evidence that ephedra supplements do not cause serious adverse events.[46] Indeed, Dr. Grover Hutchins, an anatomic pathologist with a longstanding professional focus on autopsy pathology, reviewed a number of AERs associated with the death of persons who had consumed ephedra supplements, including several Sentinel Events listed in the RAND Report.[47] Upon conclusion of this review, Dr. Hutchins expressly found that the "available information on deaths associated with ephedrine alkaloid exposure does not

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44 Id. at 7.

45 Id.

46 See Compilation of Studies at Attachment G.

47 See Grover M. Hutchins, M.D., Comments on Dietary Supplements Containing Ephedrine Alkaloids: Reopening of the Comment Period [Docket No. 95N-0304] (Apr. 3, 2003) (Attachment H).

support the suggestion that the deaths are caused or contributed to by these agents when used in the recommended manner."[48]

4. The Non-Clinical Studies Cited by FDA in Preamble Are Not Meaningful

In the preamble to the proposed rule, FDA states that several more studies have "come to light concerning the risks posed by ephedrine alkaloids."[49] However, the studies do not provide any meaningful information or evidence that ephedra supplements cause significant adverse health effects.

a. S. Bent, et al., The Relative Safety of Ephedra Compared with Other Herbal Products, 138 Ann Intern. Med. 468-72 (2003).

Comments filed independently with FDA have set forth a rigorous critique of this article.[50] According to these experts, the authors of this paper committed serious errors, misrepresenting the data as well as committing methodological flaws:

> Regarding factual misrepresentations, these authors reported that all the incidents that were tabulated under the ephedra containing product categories represented "adjudicated" reports of adverse effects. They failed to acknowledge that the vast majority of these calls undergo no process of authentication. As any poison center specialist who has ever fielded an exposure-related inquiry in a public poison center can attest, just mere fact that someone calls the poison center does not always mean that the event in question is accurately depicted or reported. In fact, these incidents are rarely verified by independent medical practitioners. More often than not, these incidents represent reports from the general public, often made anonymously, and typically accepted at face value. The data represented in TESS is a useful tool to look at the general surveillance landscape but

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48 Id. at 2.

49 68 Fed. Reg. at 10,418.

50 Richard Kingston, et al., Comments to the Secretary of HHS [Docket No. 95N-0304] (Apr. 2003).

> using the first cut of the data depicted in the TESS annual report, in an effort to draw wide sweeping and specific characterizations of a given toxicology issue is in our view, simply irresponsible.
>
> As regards other methodological flaws, the authors failed to address the fact that the data in the annual report format is not of sufficient detail so as to allow separation of reported incidents ultimately coded as "unrelated" to the product in question. Thus, the absolute number of cases relied on in the authors calculations also included cases coded with other outcomes that would suggest no relation or association to the ephedra containing product in question. The authors apparently did not adequately research the database structure. Had they done so, they would have found that the TESS annual report data is simply not presented in a format that would allow any researcher to reach the same conclusions that they reached.
>
> Lastly, there was no consideration of severity, ephedra dose, duration of use, purity, contaminants, underlying health status, or other substances concurrently consumed by individual patients represented in this dataset. Additionally, attempting to compare ephedra to other herbs/botanicals, the actions and indications of which are distinct, makes no sense from a toxicologic perspective.
>
> Shortly after the article appeared in the online version of the Annals, a letter to the editor was submitted outlining these concerns. A response from the authors and the editor is still pending.[51]

In light of these serious methodological flaws, the appropriate course of action for the Annals of Internal Medicine would be to withdraw this paper from publication. FDA should not give it any weight in its analysis of ephedra safety.

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[51] Id. at 1-2.

b. L. Morgenstern, et al., Use of Ephedra Containing Products And Risk for Hemorrhagic Stroke, 60 Neur. 132-35 (2003).

This article reviewed data relating to ephedra and the risk of hemorrhagic stroke derived from a previous study on phenylpropanolamine. Dr. Stephen Kimmel, an expert in epidemiology and cardiology, has provided comments to FDA on this article.[52] As Dr. Kimmel notes, this study has significant limitations, including lack of sufficient power, to draw any conclusions about the risk of ephedra and stroke, and the authors of the study were careful not to report such conclusions.

> The present study cannot be used to draw definitive conclusions about an association between ephedra dose and hemorrhagic stroke risk. . . . In fact, the authors of the paper themselves do not draw such a conclusion. . . . They further conclude from their study that "*Ephedra* is not associated with increased risk of hemorrhagic stroke, except ***possibly*** [my emphasis] at higher doses." They state only that "the analysis by dose suggests there ***may*** [my emphasis] be an association with use of more than 32 mg/d" but, appropriately, do not try to draw definitive conclusions from their study.[53]

c. D. Samenuk, et al., Adverse Cardiovascular Events Temporally Associated With Ma Huang, An Herbal Source of Ephedrine, 77 Mayo Clin Proc 12-16 (2002).

Dr. Kimmel also reviewed this assessment of adverse event reports.[54] Consistent with RAND and other reviews of the same reports, the authors correctly point out that the AERs at issue do not establish causality. Dr. Kimmel agrees:

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[52] Dr. Kimmel's CV is found at Attachment I.

[53] Stephen E. Kimmel, M.D., Brief Review and Hemorrhagic Stroke Paper at 3 (Jan. 27, 2003) (Review of Morgenstern article) (Attachment J).

[54] See Stephen E. Kimmel, M.D., Review of the Article "Adverse Cardiovascular Events Temporarily Associated with Ma Huang, An Herbal Source of Ephedrine" (March 30, 2003) (Attachment K).

> In summary, the AERs reviewed in the *Mayo Clinic Proceedings* paper do not establish a causal relationship between ephedra-containing products and serious cardiovascular events. These events may simply represent the background rate of myocardial infarction, stroke, and sudden death in the general population, unrelated to ephedra. There is nothing unique about these events that allow one to differentiate background events from ephedra-associated events. The most appropriate scientific studies would be those specifically designed to study the association between ephedra and cardiovascular risk, using an appropriate study design and a proper control group.[55]

In conclusion, none of the published articles mentioned in FDA's Federal Register document, other than the clinical studies supporting the safety and benefits of ephedra, have any scientific relevance to FDA's review of the safety of ephedra. FDA's assessment must be based on the clinical data. The clinical data does not have a single report of a serious adverse event. It would be illogical, and factually and scientifically indefensible, to conclude that ephedra supplements pose a significant or unreasonable risk, however that term is ultimately defined by the agency. Moreover, as these and other comments establish, the data show that ephedra supplements have important health benefits and are safe when properly labeled and taken as directed.

C. Available Evidence Demonstrates That Ephedra Supplements Provide a Public Health Benefit

The evidence that has emerged in the last six years demonstrates that ephedra supplements do, in fact, provide a public health benefit. Obesity is at an all-time high, and consumers are desperate to find ways to help themselves lose weight. Being overweight is not just an aesthetic concern: the adverse health consequences associated with excess weight is well-documented.[56] Therefore, it is vital to make available to consumers those products that will help them in their struggle to lose weight.

The authors of the RAND report concluded that "[s]hort-term use of ephedrine, ephedrine plus caffeine, or dietary supplements containing ephedra with or without herbs containing caffeine is associated with a statistically significant increase in short-term

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[55] Id. at 5.

[56] See RAND Report at 5.

weight loss (compared to placebo)."[57] Similarly, the EEC Expert Panel concluded that the "available information derived from studies of ephedrine and caffeine and dietary supplements containing ephedrine alkaloids supports the concept that dietary supplements containing ephedrine alkaloids may be useful in weight management."[58]

The numerous recent studies on ephedra supplements also indicate the supplements' benefits in helping consumers lose weight.[59] These data support the notion that ephedra supplements help consumers lose weight and, therefore, provide a public health benefit. Further, as noted above, the benefits in consuming ephedra supplements outweigh the side effects.

V. Industry Supports an Accurate Warning for Ephedra Supplements

As demonstrated by the AHPA Trade Recommendation and the October 2000 joint industry petition for warning and serving limits, industry supports an accurate warning statement for ephedra supplements. Part of the proposed labeling requirements was a warning statement, which was similar to the warning statement FDA proposed in 1997.

There is no precedent, however, for FDA's newly proposed warning statement for the principal display panel for all ephedra supplements. No other FDA regulated supplement has ever included a boxed warning on the principal display panel. Nor is the proposed warning supported by scientific evidence. Moreover, in violation of the Federal Food, Drug, and Cosmetic Act's ("FDC Act's") prohibition on misleading labeling, 21 U.S.C. § 343(a)(1), the warning misleads consumers into thinking a causal connection exists between the consumption of ephedra supplements and certain serious adverse events. FDA has stated repeatedly that such a connection is not warranted. Therefore, the proposed principal display warning should be dropped. At minimum, this warning should be revised to remove reference to FDA's receipt of reports that have not been causally linked to ephedra when consumed in accordance with the labeling for these products.

FDA's original proposed warning provided as follows:

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57 Id. at vi, 219; see also id. at 201.

58 EEC Expert Panel's Comments at 7.

59 See Attachments D and G.

> WARNING: If you are pregnant or nursing, or if you have heart disease, thyroid disease, diabetes, high blood pressure, depression or other psychiatric condition, glaucoma, difficulty in urinating, prostate enlargement, or seizure disorder consult a health care provider before using this product. Do not use if you are using monoamine oxidase inhibitors (MAOI) or for 2 weeks after stopping a MAOI drug; certain drugs for depression, psychiatric or emotional conditions; drugs for Parkinson's disease; methyldopa; or any product containing ephedrine, pseudoephedrine or phenylpropanolamine (ingredients found in allergy, asthma, cough/cold and weight control products). Stop use and call a health care professional immediately if dizziness, severe headache, rapid and/or irregular heart beat, chest pain, shortness of breath, nausea, noticeable changes in behavior, or loss of consciousness occur. Do not exceed recommended serving.[60]

This warning is substantially similar to the warning proposed by industry in 2000:

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

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[60] 62 Fed. Reg. at 30,718.

> Discontinue use and call a health care professional immediately if you experience rapid heartbeat, dizziness, severe headache, shortness of breath, or other similar symptoms.[61]

Responsible members of industry have been using the above warning on their ephedra supplements well before the petition was submitted.

Although FDA's warning is similar to the one proposed in 1997, it also contains new information not supported by scientific evidence. In particular, the warning proposed for the principal display panel cannot be justified. The warning begins with the following text: "Contains ephedrine alkaloids. Heart attack, stroke, seizure, and death have been reported after consumption of ephedrine alkaloids."[62] This warning is simply not accurate or supportable for the range of marketed ephedra products. Furthermore, this warning implies that there is a causal connection between the events and the consumption of ephedra. Why else would FDA propose to include the warning? The RAND Report dismisses this notion – the reports do not establish a causal link, and there is not a single report of any such event in any of the clinical trials. RAND also confirms that none of these events has ever occurred in a clinical trial of either ephedra or ephedrine. FDA has also recently acknowledged that no causal connection has been established between ephedra and heart attack, stroke, seizure or death. This portion of the warning is, therefore, misleading with respect to the entire ephedra market category.

If FDA will not agree to drop the principal display warning, FDA should revise this warning to make it accurate and not misleading, as follows: "Contains ephedrine alkaloids. Read and follow label directions and product warnings." There is no scientific basis for any stronger warning on the principal display panel.

VI. Conclusion

In sum, it is clear that FDA has sufficient authority under the FDC Act to regulate dietary supplements. This authority includes the power to remove products from commerce that pose an "imminent hazard" or products that pose a significant or unreasonable risk to consumers under labeled conditions of use. Prior to attempting to determine whether ephedra supplements meet the "significant or unreasonable risk" standard, however, FDA must first define the term in a formal rulemaking proceeding, or

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[61] Industry Petition at 3-4.

[62] 68 Fed. Reg. at 10,419.

at the very least, through the guidance document process, that affords the public an opportunity for input.

Once it establishes a definition of what constitutes a significant or unreasonable risk, FDA needs to evaluate the risk in light of the labeled conditions of each individual ephedra product. As set forth above, the scientific evidence shows that ephedra supplements do not pose a significant or unreasonable risk, however that term is defined when used in accordance with labeled conditions. Indeed, the Cantox Report and the RAND Report together demonstrate that (1) ephedra supplements provide a significant weight loss benefit; (2) a risk assessment of ephedra and caffeine based on human clinical data, and supported by and consistent with extensive animal toxicological data, shows that ephedra products are safe when properly labeled and formulated; and (3) AERs are not a useful tool for assessing safety, and do not establish that ephedra has caused serious adverse events.

Finally, industry supports an accurate warning for ephedra products. As discussed above, responsible members of the industry have been using the warning in the AHPA Trade Recommendation for years. Any warning imposed by FDA should be appropriately qualified to reflect what the scientific data support.

Sincerely,

A. Wes Siegner, Jr.

AWS/FKW/eam
Attachments