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Docket No. 95N-0304

The Council for Responsible Nutrition (CRN) is submitting these comments on ephedra issues under Docket No. 95N-0304 in response to the proposed rule published in the Federal Register (68 FR 10417) dated March 5, 2003.

FDA raised four issues for comment: (1) the relevance of the 1997 proposed rule (62 FR 30678), (2) the newly proposed warning statements in 68 FR 10417, (3) whether current scientific evidence, including the Rand Report that was released by FDA on February 28, 2003, supports the conclusion that dietary supplements containing ephedrine alkaloids present a "significant or unreasonable risk of illness or injury," and (4) what additional legislative authorities, if any, would be necessary or appropriate to enable FDA to address this issue effectively.

CRN's comments are arranged in four sections corresponding to the issues identified in the previous paragraph.

SECTION 1—Comment responding to the reopening of the comment period on the 1997 proposed rule

Issue 1—Dosage limits: In 1997, FDA proposed a new 21 CFR Sec. 111.100 that would have deemed adulterated under sections 402(a)(1) and 402(f)(1)(A) of the Federal Food, Drug, and Cosmetic Act (FDCA) any dietary supplement containing 8 mg or more ephedrine alkaloids per serving or 24 mg or more ephedrine alkaloids per day. In 2000 (65 FR 17474), FDA withdrew the proposed potency restrictions in the 1997 proposal.

The new proposed rule does not specify specific potency limits. Instead, the agency asks whether dietary supplement products containing ephedrine alkaloids present a "significant or unreasonable risk of illness or injury," and therefore are adulterated.

CRN comment: This 1997 proposal was not supported by scientific evidence that these quantities of ephedrine alkaloids present a significant or unreasonable risk of illness or injury. Newer scientific evidence, including the Rand report, does not support the 8 and 24 mg adulteration thresholds proposed by FDA in 1997. Due to the withdrawal in 2000, FDA has no current proposal for potency limits on ephedrine alkaloids in dietary supplements. However, the issue of dosage limits will be discussed in Section 3 of this comment.

The General Accounting Office (GAO) issued a report in 1999 that criticized FDA's dependence on adverse event reports (AERs) to identify the proposed dosage limits, indicating that FDA should perform a reevaluation of the scientific evidence. In the interim since FDA's withdrawal in 2000 of the dosage limits proposed in 1997, no other approach to identification of appropriate dosage limits has been offered by FDA. The quantitative risk assessment performed by Cantox Health Sciences International is one scientifically valid approach (see Section 3 of this comment).

Dosage limits could be adopted, based on sound science. FDA's 1997 proposal for dosage limits and other requirements for ephedra failed because the recommended limits were not based on sound science. The GAO report that drew this conclusion did not suggest that no dosage limits could be established, but only that the manner in which FDA went about selecting its particular proposed limit was not scientifically sound. Other alternatives existed at the time and still exist, by which FDA could establish dosage limits by regulation. The strongest evidence would be derived from a quantitative risk assessment such as the one prepared by CANTOX for CRN. The Rand report is a qualitative review of the scientific evidence but does not incorporate the kind of quantitative evaluation needed for a full risk assessment. Rand or another qualified contractor could conduct such a risk assessment, if FDA chooses not to rely on the CANTOX report prepared for CRN, and a valid risk assessment such as this could provide the basis for scientifically supportable dosage limits. The preparation of a risk assessment and the drawing of conclusions regarding upper limits to be recommended involve some matters of scientific judgment, including the selection of the criteria for the No Observed Adverse Effect Level (NOAEL) and the selection of the uncertainty factor to be applied in deriving a recommended Upper Level of Tolerable Intake (UL) for the general population or for the population defined by the exclusion criteria that may be specified. Preparation of the CANTOX report took about a year, but in view of fact that this assessment and the Rand report now exist to draw upon, preparation of a new risk assessment by either of these firms or by some other firm may be feasible within a shorter amount of time. CRN would fully support such an approach to establishing a scientifically sound dosage limit.

Issue 2—Proposed label warning: The 1997 proposed rule included a detailed warning statement that would have been required on the label.

CRN comment: CRN fully supports a requirement for a warning label on ephedra products. The 1997 proposed rule, however, included labeling requirements that were less informative than, and have now been superceded by the contents of warnings

described in the Cantox Report, the "industry standard" in the October 25, 2000 industry petition to FDA, and the label warning newly proposed in 68 FR 10417. Thus, CRN recommends no further consideration of the warning in the 1997 proposed rule.

CRN's recommendations on warning labels will be discussed in Section 2 of this comment.

SECTION 2—Comments on the newly proposed warning statements

In 68 FR 10417, FDA has proposed two warning statements for ephedra product labels: (1) a principal display panel (PDP) statement giving a summary, but extended, description of the dangers reported in relation to ephedra use and providing some contraindication information, and (2) an outer package label warning giving bulleted detail of the same information.

CRN comment:

CRN supports appropriate label warnings when necessary to help consumers use products safely, and section 403(s) of the FDCA specifically recognized the inclusion of warnings in dietary supplement labeling. The exclusion and contraindication criteria used in clinical trials provide an excellent starting point for the development of effective warning statements and instructions for use.

The Cantox report (submitted to Docket No. 00N-1200 on December 20, 2000, and available at *http://www.crnusa.org/cantoxreportindex.html*) identified conditions of safe use for ephedra. These conditions include dosage limits, limitation of duration of use, minimum age for users, exclusion of persons with health conditions that increase the risk of adverse effects, and cautions against simultaneous use of ephedra and a number of other substances, including drugs. To achieve the restrictions described in the Cantox report, CRN recommends a strong and conspicuous label warning equivalent to or perhaps exceeding the following:

> *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.*

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

The primary warning label issue is whether it is reasonable to expect consumers to read and follow the label instructions and warning to achieve the conditions of safe use. If such expectation is reasonable, the products containing ephedra with the safe dosage range and labeled appropriately do not create a "significant and unreasonable risk of illness or injury" and are not adulterated under 402(a)(1) or 402(f)(1)(A) if they bear the required label warning statement.

CRN believes that it is reasonable to expect consumers to read and comply with dosage limits and warning labels. FDA has reached similar conclusions where misuse of products or ingredients can produce severe adverse effects.

For certain foods, FDA requires warning (21 CFR 101.17). See the box below.

a) Eye hazards related to self-pressurized containers,
b) Inhalation hazard related to halocarbon or hydrocarbon propellants in food containers,
c) [not misuse]
d) Health hazards related to very low calorie protein products,
e) Pediatric accidental overdose hazards related to iron-containing supplement products,
f) [statutory and now repealed], and
g) Phenylalanine content of products containing the artificial sweetener Aspartame, directed to phenylketonurics.

None of these warnings is required to be placed in the PDP.

None of the warnings required on the labeling of over-the-counter (OTC) drugs is required to be placed in the PDP (21 CFR 201.63, 201.64, and 201.66). Warnings on OTC drugs must be under a heading titled "warning(s)" (21 CFR 201.66)(c)(5). The warning heading is part of the Drug Facts format.

The regulations developed by the Consumer Product Safety Commission (CPSC) under the Federal Hazardous Substances Act (FHSA) (originally enforced by FDA) and the Environmental Protection Agency (EPA) for pesticides used by consumers under the Federal Insecticide, Rodenticide and Fungicide Act (FIFRA) use a format where the PDP contains a signal word and identification of the principal hazard, and a reference to where the complete precautionary information may be found on the label. See 16 C.F.R. Part 1500 and 40 C.F.R. Part 156.

As a result, there has been extensive experience with this format that (1) boldly catches the attention of consumers and (2) refers them to complete information provided in a

single location. This practice has successfully relied on consumers to read and comply with a strong and conspicuous warning statement on the label. Thus, it is appropriate and necessary to identify the wording and other aspects of the label warning that would be most likely to produce consumer compliance with the conditions of safe use for ephedra.

In this regard, CRN has carefully considered FDA's proposal for repetitive warning statements on the principal display panel (PDP) and the outer product label or in product labeling that is an integral part of outer product packaging.

PDP warning statement:
CRN is concerned that too much detailed information at this location would dilute and diminish the impact of the warning statement, and is inconsistent with the "signal/refer/explain" format successfully used with numerous hazardous products. To reduce this problem, CRN recommends a PDP warning statement equivalent to the following examples:

Example 1:

WARNING: Misuse of ephedra is dangerous. Some people should not use Ephedra. Do not use this product unless you have read, understood, and comply with the detailed directions and warnings on [label location].

Example 2:

WARNING: Misuse can be dangerous. Some people should not use Ephedra. Read and follow directions. Do not misuse. See directions and warnings on [label location] .

The PDP warning statement must be bold, conspicuous and easy to understand. Further, it should disclose the presence of ephedra in the product. Consumer quotes from recent media articles reveal consumer misunderstanding regarding when a product contains ephedra.

Outer label warning statement:
For the detailed information about consequences of misuse and restrictions of use, CRN recommends combining and retaining detailed information about ephedra in the two warning statements that FDA proposed, by incorporating them into a single statement to be required for the outer product label, and to be referred to in the PDP warning statement.

Ephedra products that do not bear all required label warning statement(s) would be deemed both misbranded and adulterated, i.e., the absence of an adequate warning would pose a "significant or unreasonable risk of illness or injury" under labeled conditions of use.

SECTION 3—Comments on whether the scientific evidence shows that dietary supplement products containing ephedrine alkaloids present "significant or unreasonable risk of illness or injury"

FDA requested comments on whether the available scientific evidence, including the Rand report, supports a conclusion that all ephedra products present a significant or unreasonable risk.

CRN comment:

A valid and quantitative scientific process is needed to identify intakes and conditions of intake, if any, that do not create significant or unreasonable risk. The Rand Report does not take a sufficiently quantitative approach in its review of the data relevant to the evaluation of ephedra safety.

The Cantox report (submitted to Docket No. 00N-1200 on December 20, 2000, and available at *http://www.crnusa.org/cantoxreportindex.html*) describes a quantitative risk assessment, which is the most appropriate approach to the evaluation of the safety of any dietary ingredient. Thus, this approach is appropriate for use in evaluation of ephedra products used in dietary supplements.

The Cantox risk assessment evaluated all data from all sources—biochemical studies of the ephedrine alkaloids, the pharmacokinetics of the ephedrine and related alkaloids, animal toxicology studies, human clinical trials, case reports, and adverse event reports (AERs) filed with FDA. The Cantox report concluded that although ephedra contains alkaloids that cause effects that could become adverse, some dosage ranges are safe for healthy persons. The Cantox report concluded that the numerous weaknesses and general limitations in AERs prevent any conclusion of causality, even when the temporal relationship and character of the event makes it plausible that ephedra consumption was the causative factor. In the face of these weaknesses and limitations, Cantox based its safety assessment on the available clinical trial data.

In the Cantox report, the Boozer et al. (2002) clinical trial data formed the central but by no means only basis of the conclusion. This clinical trial involved administration of 90 mg (30 mg three times per day) of ephedrine alkaloids in ephedra together with 192 mg (64 mg three times per day) of caffeine from an herbal source. Moreover, the research protocol did not prohibit consumption of coffee or other sources of caffeine or related methylxanthines. In the Cantox report, the scientifically identified conditions of safe use of ephedra as a dietary supplement include:

- Intake limits of 90 mg per day and 30 mg per single serving for ephedrine alkaloids from ephedra.
- A six-month maximum duration of use.
- No use by persons under 18 years of age.

- A strong and conspicuous warning label with the following or equivalent language to implement necessary exclusions, contraindications, and instructions for use to correspond with those utilized in several clinical trials:

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

Cantox and CRN view this warning label, or a stronger warning that includes both PDP and outer label placements, as an essential component of the conditions of safe use for ephedra. The PDP and outer label warnings should have the characteristics described in Section 2 of this comment.

Although the Cantox report was completed in December 2000, it included and considered the clinical trial data that have been more recently published by Boozer et al., 2002. These data and the authors' interpretations were available in a detailed published abstract and public presentation in October 2000.

The conditions of safe use identified in the Cantox report are closely similar to the "industry standard" recommendations of dosage limits and warning recommendations, as described in an industry petition to FDA on October 25, 2000. These "industry standard" conditions of safe use include a requirement for a warning equivalent to that recommended in the Cantox Report, and a maximum dosage of 25 mg per of ephedrine alkaloids per serving and 100 mg per day. In comparison to the CRN policy based on the Cantox Report, the industry standard is slightly more restrictive for each dose (25 mg, instead of the 30 mg identified by Cantox) but allows a fourth dose each day, resulting in a slightly higher daily total (100 mg, rather than the 90 mg identified by Cantox). Based on the pharmacokinetics and physiological effects of the ephedrine alkaloids in ephedra, these dosage patterns and quantities would have indistinguishable biological effects (Letter to Secretary Thompson, dated April 2, 2002).

The Rand report[1]

The Rand report should not change the conclusion on whether there is "significant or unreasonable risk" from consumption of ephedra supplements. The RAND meta-analysis showing increased risk of mild to moderate adverse effects does not, by itself, justify a conclusion of "significant or unreasonable risk. " The total clinical trial data are sufficient to show that the risk of a major adverse event is less than 1 in 1,000.

Upon detailed examination, several problems in scientific methodology and/or interpretation are apparent in the Rand report. The report includes methodological biases[2] that lead to particular conclusions that are not justified by the evidence.

Major points

A. Not all appropriate and useful questions were asked, and the answers were inconsistent. The questions in the Summary (pages xii-xvii) should include: "Is ephedrine a good surrogate for ephedra in evaluation and prediction of the effects ephedra?" This question should be separately considered under Weight Loss, Athletic Performance, and Safety Assessment. The discussion on this point in a later section gives an answer of "yes" for weight loss and safety assessment, but this extrapolation is not made for athletic performance. Instead, the report asserts that there are no data on the effects of ephedra itself on athletic performance. Note that the Summary section (page xvi) on weight loss states, "There is no evidence that the effect of ephedra-containing dietary supplements with herbs containing caffeine differs from that of ephedrine plus caffeine."

B. Methodology selection is biased in ways that avoid certain conclusions strongly supported by the scientific evidence.

i. In the assessment of efficacy for weight loss, the sixth type of comparison, that on ephedra plus herbs that contain caffeine, was omitted because it was represented by a single clinical trial, and thus could not accommodate calculation of an "effect size" as defined in this report (difference in weight loss divided by the standard deviation). This unfortunate definition resulted in the *de facto* elimination of and failure to consider the data from the Boozer et al. (2002) clinical trial. This study is arguably the strongest and most relevant of

[1] Shekelle P, Morton S, Maglione M, t al. Ephedra and Ephedrine for Weight Loss and Athletic Performance Enhancement: Clinical Efficacy and Side Effects. Evidence Report/Technology Assessment No. 76 (Prepared by Southern California Evidence-based Practice Center, RAND, under contract NO 290-97-0001, Task Order No. 9) AHRQ Publication No. 03-E022. Rockville, MD: Agency for Healthcare Research and Quality, February 2003. Downloaded for this critique and comment to the Docket from: http://www.fda.gov/OHRMS/DOCKETS/98fr/95n-0304-bkg0003-ref-07-01-index.htm.

[2] The term "bias" is used in this comment to connote methodological choices that increase the likelihood of a particular outcome, rather than other outcomes that are equally supported by the evidence. The term is not used to imply intent.

the clinical trials on the benefit and safety of ephedra, and it strongly supports both benefit and safety of ephedra with a daily consumption 90 mg of ephedrine alkaloids from ephedra and 192 mg of caffeine per day from an herbal source, under specified conditions of use. Selection of comparison methods that avoided use of these data cannot be justified on a scientific basis, and leads to biased conclusions.

ii. The dose-response assessment of the clinical trial data in the safety assessment methodology is biased toward a conclusion that ephedra is hazardous. The methodology defines three dosage ranges ("low" is 10-20 mg, "medium" is 40-90 mg, and "high" is 100-150 mg), but arbitrarily excludes the medium range from the comparison. The resulting comparison of low dosages with high dosages leads to an overly generalized conclusion that is related to a two to three fold increase in risk of certain adverse effects, without reference to the dosages involved. It is most noteworthy that the medium range that was eliminated from this comparison encompassed the 90 mg/day dosage used in the Boozer et al (2002) clinical trial, without significant adverse effects. This study was identified as the critical dataset in the quantitative risk assessment by Cantox Health Sciences International. There is no scientific justification for this failure to consider the safety of the medium range doses of ephedrine alkaloids from ephedra.

iii. The discussion of the dosages, as ephedrine alkaloids in ephedra or as purified ephedrine, associated with various case reports and adverse event reports related to ephedra or ephedrine does not provide any critical evaluation of dose-response relationship, or lack thereof. There are at least two major issues: (1) credibility of the dosage data, and (2) lack of any believable dose- response relationship. The reported dosages of ephedrine alkaloids from ephedra or synthetic ephedrine for some types of adverse event cover a very wide range: deaths, 3.3 to 306 mg; stroke 1.3 to 160 mg; other cardiovascular events, 24 to 2,000 mg; and psychiatric effects, 5.6 to 28,000 mg. This lack of any homogeneity or predictability in the dose-response relationship violates one of the basic principles of toxicology—the stronger the dose the stronger the effect—and therefore suggests either or both of two possible explanations: (1) there is no causal relationship between the ephedra or ephedrine intake and the adverse effect outcome, or (2) that the dosages are not accurately reported. In many of the cases, the dosage is listed as "not described" or "unknown." One case (13408) is listed as a possibly sentinel event with a listed dosage of "not described." This case is an excellent example of the unreliability of reported dosages that do not have objective verification. Details provided in the Docket include the patient's admission to the Food and Drug Administration investigator that he took "a handful at the time several times a day." Contrary to the Rand Report statement, this case does include some description of the dosage, but that description almost certainly indicates an intake that was recklessly far above that on the label instructions.

iv. The review and analysis in the Rand Report was completed before the prepublication release (in January 2003) of an article by Bent S, et al. scheduled for publication in the March 18 issue of *Annals of Internal Medicine*. This article cites data indicating that in 2001 ephedra accounted for 64 percent of the adverse event reports for all herbal supplements, although it represented only 0.82 percent of the sales in that category. The calculated relative risk was 78-fold (64% ÷ 0.82%) for ephedra supplements, as compared with other herbal supplements. This report, however, cited sales data that captured only a small fraction of supplement sales. Other data from the *Nutrition Business Journal* indicates that in the total supplement marketplace, ephedra amounted to 35 percent of herbal supplement sales in 2001. Thus, the proper relative risk value is identified as 1.8 (64% ÷ 35%). It is noteworthy that this relative recalculated risk value is in the same range as the risk for mild to moderate adverse effects of ephedra consumption as identified in the Rand Report (odds ratios of 2.1 to 3.6, in Table 19) through meta-analysis of the controlled clinical trials. Certainly, no valid scientific data support anything approaching a 78-fold increase in risk. [How does the Rand Report's exclusion of this scientifically flawed study affect the validity of the methodology of the Rand Report? I agree that this study should be exposed for what it is, but if it was not included in the Rand Report, how does it affect it? Perhaps this would be better addressed in a separate heading, as it is more relevant to a discussion of FDA's analysis beyond the Rand Report]

C. Contributions of the Rand Report to understanding of the scientific evidence on the benefits and risks of ephedra

The Rand Report contributes to scientific understanding on the safety of ephedra, giving an estimate of the relative risk of mild to moderate adverse effects in clinical trials. Meta-analysis methodology is a powerful addition to the assessment of the effects of ephedra, but certain methodological choices, including the selection of meta-analysis itself, hamper the reports' usefulness in important ways.

i. Benefits--the method of calculation of effect size for benefit in weight loss caused the longest term and perhaps best controlled clinical trial (Boozer et al., 2002) not to be included in estimation of treatment size.

ii. Safety—although the dosage ranges identified (low, 10-20 mg; medium, 40-90 mg; and high, 100-150 mg) were reasonable, the arbitrary elimination of the medium range from the comparison of effects increases the likelihood of a conclusion that ephedra is harmful. The report does not effectively and directly address whether ephedra is safe in clinical trials in the medium dosage range. This is a critical flaw in that it eliminates the most scientific approach available for assessment of the safety of the usually recommended dosages in most ephedra products. Correspondingly, elimination of the medium dose range from the comparisons precluded any assessment of the degree of agreement or

disagreement between the Rand report and the Cantox quantitative risk assessment.

The significant and useful new contributions of the Rand Report on ephedra safety assessment include (1) meta-analysis for an increase in risk of mild to moderate adverse effects in clinical trials, (2) meta-analysis and power calculation from the collection of clinical trials that demonstrated any risk of serious adverse effects to be less than 1 in 1,000, and (3) publication of a summary of the adverse event reports released by Metabolife.

The conclusions from the Rand report are consistent with those in the Cantox report, as follows:

- The clinical trials do not show any risk of major adverse effects by ephedra or ephedrine alkaloids at the intakes administered in the ephedra clinical trials, even when caffeine or a botanical source of caffeine is co-administered.
- The increased risk of mild to moderate adverse effects in the high intake range (100-150 mg of ephedrine alkaloids per day) of the clinical trials identified by the Rand report is consistent with the Cantox identification of a Lowest Adverse Effect Level (LOAEL) of 150 mg of ephedrine per day.
- The case reports and adverse event reports (AERs) do not establish causality for the major adverse events.

CRN Conclusion: Interpretation of the total scientific data, including the Rand and Cantox reports, does not support a determination of "significant or unreasonable risk" when Ephedra products are used in accordance with the Industry Standard directions and warning.

In its White Paper, the Food and Drug Administration concluded correctly, from all the evidence including the Rand Report, that "there is no smoking gun" on a causal relationship between ephedra and reported major adverse effects. Through meta-analysis, the Rand report identified some increase in mild to moderate adverse effects.

Mild to moderate adverse effects do not necessarily indicate "significant or unreasonable risk." The clinical trials, the Rand report, the Cantox report, and the AERs do not establish any increased risk of major adverse effects in persons who meet the exclusions, contraindications, and instructions for use suggested in the Cantox report and used on most ephedra products at this time. Because of the potential for serious adverse effects and the undesirability of mild to moderate adverse effects, FDA should use the rulemaking now underway to require appropriate, strong warning statements and conditions for use on the label and labeling, compatible with those identified in the Cantox report.

The question of "significant or unreasonable risk" must be answered in a quantitative manner, for specified conditions of use. The proposed rule inexplicably fails to ask the appropriate questions regarding "how much" and "what circumstances." The Cantox report provides scientifically based answers to these questions. Ephedrine alkaloids

intakes of 30 mg per dose up to a maximum of 90 mg per day do not present significant or unreasonable risk in persons who read and follow the suggested label instructions and warnings. The PDP and outer label warnings proposed by FDA can be constructed to be sufficient for this purpose.

SECTION 4—Comments on additional legislative authorities

In 68 FR 10417, FDA asked for comments "on what additional legislative authorities, if any, would be necessary or appropriate to enable FDA to address this [ephedra] issue most effectively."

CRN comment:

In their news conference on February 28, 2003, Secretary Thompson and Commissioner McClellan made it clear that they wish to consider whether "premarket approval" is needed and appropriate for ephedra products.

CRN believes that current law provides ample authority for the Secretary or the Commissioner to take the necessary steps to assure the safety of all dietary supplement ingredients, including ephedra, for the reasons described below.

FDA's current authorities on the safety of dietary ingredients used in dietary supplements

FDA already has ample authority to regulate ephedra for safety, based on the existing law:

- Sec. 402(a)(1) states that a food is adulterated if it—
  "bears or contains any poisonous or deleterious substance which may render it injurious to health; but in case the substance is not an added substance such food shall not be considered adulterated under this clause if the quantity of such substance in such food does not ordinarily render in injurious to health."
- Sec. 402(f)(1) states that a dietary supplement is adulterated if it—
  (A) "presents a significant risk of illness or injury under—
  (i) conditions of use recommended or suggested in labeling, or
  (ii) if no conditions of use are suggested or recommended in the labeling, under ordinary conditions of use;
  (B) is a new dietary ingredient for which there is inadequate information to provide a reasonable assurance that such ingredient does not present a significant or unreasonable risk of illness or injury;
  (C) the Secretary declares to pose an imminent hazard to public health or safety....
  (D) is or contains a dietary ingredient that renders it adulterated under paragraph [402](a)(1) under the condition of use recommended or suggested in the labeling of such dietary supplement.

A dietary ingredient used in a dietary supplement before October 15, 1994 is excluded from the public safety analysis required for "new dietary ingredients." Rather, FDA must take the initiative to show that it is adulterated under one or more of the above provisions. This presumption of the safety of "grandfathered" ingredients is often misrepresented as a new type of lack of control imposed by DSHEA. Such comments almost invariably fail to recognize that an analogous provision was represented in the Generally Recognized As Safe (GRAS) exclusion from premarket approval in the Food Additives Amendment of 1958, which added section 201(s) to the FDCA. Moreover, the GRAS exception (201(s)) allows such ingredients to be marketed without FDA approval or notification based on a self-determination of GRAS by the manufacturer.

FDA's authority to act against unsafe dietary supplements includes provisions to deem the ingredient adulterated under the following conditions:

Old ingredients

- 402(a)(1): the "may render injurious" or "ordinarily injurious" standards
- 402(f)(1)(A): the "significant or unreasonable risk" standard added by DSHEA
- 402(f)(1)(C): the "imminent hazard" authority made explicit by DSHEA

New Ingredients

- 402(f)(1)(B): adulterated if "there is inadequate information to provide reasonable assurance that such ingredient does not present a significant or unreasonable risk"
- 413(a)(2): adulterated if, at least 75 days before marketing the ingredient, the manufacturer has not provided written notice providing the basis on which the ingredient "will reasonably be expected to be safe."

Thus, current legislation provides the government two approaches to assure the safety of dietary ingredients, including ephedra:

- For "old" dietary ingredients FDA may undertake rulemaking to develop a regulation that, if appropriate and adequate scientific support is available, finds ephedra to present a significant or unreasonable risk, and use this finding to declare it adulterated, and the Secretary may declare it to present an imminent hazard (and then take action under sections 554 and 556 of title 5, U.S. Code, to affirm or withdraw the declaration). Although no specific procedure is provided for the Secretary's action, the Secretary, in applying the same authority with respect to drugs (see section 505(e)(X) of the FDCA, has sought a public analysis of the risk of harm in order to avoid the action being considered in violation of the Administrative Procedure Act as "arbitrary and capricious."
- For new dietary ingredients, FDA may deem them adulterated if no 75-day notice has been filed, or, if a notice has been filed, FDA may disagree with the notice and notify the manufacturer that it will take regulatory action if the ingredient is marketed.

Ephedra is "grandfathered" as an "old" dietary ingredient. Therefore, new dietary ingredient notification does not apply, but the government has the authority to declare it

to be an imminent hazard, or to undertake rulemaking to deem it adulterated if presents significant or unreasonable risk.

If the Secretary were scientifically persuaded that ephedra presents an imminent hazard, he could declare it to be an imminent hazard. The Cantox and Rand reports do not appear to support such a determination. Recognizing this, FDA has undertaken notice-and-comment rulemaking to present the scientific evidence, and ask for comments on four issues.

Legal analysis of some issues relating to FDA authority

CRN requested legal analysis from its counsel Peter Barton Hutt, of Covington & Burling regarding some specific issues that have been raised regarding FDA's authority under DSHEA. These include the practical impact of the imminent hazard authority, the effect of the requirement for a hearing, the usual situation regarding FDA's burden of proof, and the implications of the *de novo* review. Mr. Hutt's analysis on these points follows:

> 1. Imminent hazard. Under Section 402(f)(1)(C) of the Federal Food, Drug, and Cosmetic Act (FD&C), as added by the Dietary Supplement Health and Education Act (DSHEA) of 1994, the Secretary has the authority to declare a dietary supplement or dietary ingredient "to pose an imminent hazard to public health or safety." This authority may not be delegated. The Secretary is required to initiate a proceeding to affirm or withdraw the declaration promptly after the determination of an imminent hazard is made.
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> The only reasonable way to interpret and apply this provision is that the dietary supplement or dietary ingredient remains banned, and cannot be marketed, pending the outcome of the administrative proceeding under the APA. First, there would be no reason to require an immediate administrative proceeding if there were not an immediate ban. Second, the existing FDA definition of an imminent hazard in 21 C.F.R. 2.5 provides that one element of the definition of an imminent hazard is that the situation should not be permitted to continue while a hearing or other formal proceeding is being held. This is the way that the imminent hazard provision has been applied to new drugs under Section 505(e) of the FD&C Act, as affirmed in the only litigated case, Forsham v. Califano, 442 F. Supp. 203 (D.D.C. 1997). In practice, the Secretary has always requested an evaluation from FDA, and the affected companies have always had an opportunity informally to make their position known to FDA and the Secretary, but this has happened very quickly and is not a substitute for the formal administrative hearing required by the statute.
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> 2. Section 402(f)(2) of the FD&C Act states that, before FDA may request the Department of Justice (DOJ) to bring a civil action to enforce the provision that prohibits a dietary supplement

or dietary ingredient that presents a significant or unreasonable risk of illness or injury, the agency must give appropriate notice and opportunity to present oral and written arguments with regard to the matter at least ten days before the agency requests DOJ action. The civil proceedings that would be involved would be seizure or injunction actions. This would not include a declaration of imminent hazard, because this is not a judicial proceeding instituted by the DOJ. There is virtually no potential for the presentation of views to degenerate into a lengthy proceeding because FDA has established a quick and efficient "regulatory hearing" under 21 C.F.R. part 16 for this type of proceeding. FDA has not yet amended part 16 to cross-reference Section 402(f)(2), but it would be easy for the agency to do this. (This is another example of where the existing statutes and regulations give FDA all the authority it needs, and the agency still is unable to implement them.) Nonetheless, FDA could immediately use part 16 even before adding a formal cross-reference.

3. Burden of proof. Section 402(f)(1) of the FD&C Act states that FDA bears the burden of proof in showing that a dietary supplement is adulterated. It is not at all unusual for FDA to bear the burden of proof in any number of adulteration cases. If FDA contends that a food contains a poisonous or deleterious substance, it must bear the burden of proof. If FDA contends that a food substance is not generally recognized as safe (GRAS), it must bear the burden of proof. If FDA contends that a food additive is being used outside the approved food additive regulation, it must bear the burden of proof. Any number of other examples could also be given. Thus, it is not surprising that Congress determined that FDA must also bear the burden of proof with respect to the adulteration of a dietary supplement or dietary ingredient.

4. De novo determination. Section 402(f)(1) of the FD&C Act provides that the court shall decide the issue of adulteration of a dietary supplement or dietary ingredient "on a de novo basis." This is in part a traditional requirement and in part a novel requirement, depending upon how FDA implements the dietary supplement adulteration provisions in Section 402(f)(1).

If FDA were to proceed directly in court with civil or criminal litigation contending that a particular dietary supplement is adulterated, the agency would unquestionably bear the burden of proof (as discussed above) and the court would unquestionably decide the matter on a de novo basis. This is how FDA litigation has always been conducted with respect to adulteration issues, and presents no new policy question.

If FDA were to pursue the matter through rulemaking, however, this provision would present a novel approach. Under standard principles of administrative law, once FDA has promulgated a

regulation determining that a dietary supplement is adulterated, a reviewing court would be obligated to sustain the FDA position unless that position was determined to be arbitrary or capricious. Under the Supreme Court decision in Citizens to Preserve Overton Park, Inc. v. Volpe, 401 U.S. 402 (1971), the reviewing court would go no further than the administrative record and would not make its own de novo determination.* Under the DSHEA provision, however, a reviewing court would make its own de novo determination on the adulteration issue, and thus it would make no difference whether FDA brought its case initially in court or whether it proceeded through rulemaking that was subsequently challenged in court.

This provision undoubtedly reflects the deep distrust of FDA by Congress in 1994 on dietary supplement issues, as a result of the repeated agency statements in the early 1990s that FDA intended to wage a campaign against dietary supplement products and ingredients. Congress concluded that the agency could not be trusted to make an unbiased, objective, and science-based determination on these matters, and therefore entrusted the decision to a reviewing court on a *de novo* basis.

Summary comment to Docket No. 95N-0304

This comment is responsive on the four issues in the proposed rule on which FDA asked for comments. In summary, CRN's comments on these four issues are:

1. The 1997 proposed rule—it has been superceded by more recent scientific evidence and recommendations.

2. Warning labels—CRN supports strong and conspicuous warnings on ephedra products, including a brief but strong warning on the PDP, in accordance with the language suggested in these comments.

3. The scientific evidence for "significant or unreasonable risk"—the Rand report is limited by methodological issues and the report does not provide a basis for this conclusion; AERs are of limited value and do not support this conclusion; the Cantox report identifies conditions of safe use that include a requirement for exclusions, contraindications, and instructions for use that can be achieved by appropriate labeling. FDA should propose specific limits based on risk assessment that relies heavily on clinical trial data to identify intakes that do no present significant or unreasonable risk.

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* Chevron U.S.A. Inc. v. Natural Resources Defense Council, Inc., 467 U.S. 837 (1984), which requires judicial deference to an agency's interpretation of a statute when the statute is not clear on its face, is not applicable here.

4. Need for additional legislative authority—the government has ample authority to deal with the safety of ephedra, but has been slow to take action under this authority; premarket approval procedures are not a guarantee of safety and are not necessary to assure the safety of ephedra.

Sincerely,

John Hathcock, Ph.D.
Vice President