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February 4, 2004

REVISIONS
2-4-04

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 119

[Docket No. 1995N-0304]

RIN 0910-AA59

**Final Rule Declaring Dietary Supplements Containing Ephedrine Alkaloids
Adulterated Because They Present an Unreasonable Risk**

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA, we, our) is issuing a final regulation declaring dietary supplements containing ephedrine alkaloids adulterated under the Federal Food, Drug, and Cosmetic Act (the act) because they present an unreasonable risk of illness or injury under the conditions of use recommended or suggested in labeling, or if no conditions of use are suggested or recommended in labeling, under ordinary conditions of use. We are taking this action based upon the well-known pharmacology of ephedrine alkaloids, the peer-reviewed scientific literature on the effects of ephedrine alkaloids, and the adverse events reported to have occurred in individuals following consumption of dietary supplements containing ephedrine alkaloids.

DATES: This rule is effective on *[insert date 60 days after date of publication in the Federal Register]*.

FOR FURTHER INFORMATION CONTACT: Wayne Amchin, Center for Food Safety and Applied Nutrition (HFS-007), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-6733.

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I. Introduction

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A. Why Have We Concluded That Dietary Supplements Containing Ephedrine Alkaloids Present an Unreasonable Risk?

We conclude that dietary supplements containing ephedrine alkaloids are adulterated under section 402(f)(1)(A) (21 U.S.C. 342(f)(1)(A)) of the act because they present an unreasonable risk of illness or injury under the conditions of use recommended or suggested in labeling, or if no conditions of use are suggested or recommended in labeling, under ordinary conditions of use. Dietary supplements containing ephedrine alkaloids are most often used for weight loss, energy, or to enhance athletic performance.

Chinese *Ephedra*, and ephedron are several names used for botanical ingredients, primarily from *Ephedra sinica* Stapf, *Ephedra equisetina* Bunge, *Ephedra intermedia* var. *tibetica* Stapf and *Ephedra distachya* L. (the *Ephedras*), that are sources of ephedrine alkaloids (Refs. 1, 6, and 7). Other plant sources that contain ephedrine alkaloids include *Sida cordifolia* L. and *Pinellia ternata* (Thunb.) Makino (Ref. 8 and 9). Common names that have been used for the various plants that contain ephedrine alkaloids include sea grape, yellow horse, joint fir, popotillo, and country mallow. The names desert herb, squaw tea, Brigham tea, and Mormon tea refer to North American species of *Ephedra* that do not contain ephedrine alkaloids but have been misused to identify ephedrine alkaloid containing ingredients. Although the proportions of the various ephedrine alkaloids in botanical species vary from one species to another, in most species used commercially, ephedrine is typically the predominant alkaloid in the raw material (Ref. 10).

Dietary supplements containing ephedrine alkaloids are widely sold in the United States (Refs. 11 through 13).¹ Over the last decade, dietary supplements containing ephedrine alkaloids have been labeled and used primarily for weight loss, energy, or to enhance athletic performance. Additional scientific evidence, and numerous reports of serious adverse events, including death, following consumption of dietary supplements containing ephedrine alkaloids, have raised concerns about their safety. Consequently, we have taken a number of actions in an attempt to protect the public from the risks of these products.

¹ We use the term “dietary supplements containing ephedrine alkaloids” in this final rule to refer to dietary supplements containing botanical sources of ephedrine alkaloids. We use the term “ephedra” to refer to botanical sources of ephedrine alkaloids, whether derived from a member of the *Ephedra* genus or another botanical, such as *Sida cordifolia* L. or *Pinellia ternata* (Thunb.) Makino. We use the term “*Ephedra*” to refer specifically to the *Ephedra* genus of plants.

laxatives, and diuretics, because these ingredients can alter electrolyte levels and increase the risk of arrhythmias. One comment, citing a study by Haller et al., contended that the apparent causal role of ephedrine alkaloids in severe adverse effects could be related to the additive stimulant effects of caffeine (Ref. 34). One comment submitted by a manufacturer attributed the good safety record of its product to, among other reasons, the absence of caffeine and other stimulants.

(Response) We agree that dietary supplements containing ephedrine alkaloids present risks of adverse physiological and pharmacological effects. Based on the best available scientific data and the known pharmacology of ephedrine alkaloids and other sympathomimetics, ephedrine alkaloids—including dietary supplements containing ephedrine alkaloids—pose short-term and long-term risks. This is clearest in long-term use, where increased blood pressure in any population will clearly increase the risk of stroke, heart attack, and death, but there is also evidence of increased risk from shorter-term use in patients with heart failure or underlying coronary artery disease.

Ephedrine alkaloids are members of a large family of sympathomimetic compounds that include dobutamine and amphetamine. Members of this family increase blood pressure and heart rate by binding to alpha- and beta-adrenergic receptors present in many parts of the body, including the heart and blood vessels (Refs. 35³⁶ and 37). These compounds are called sympathomimetics because they mimic the effects of epinephrine and norepinephrine, which occur naturally in the human body. In addition to their direct pharmacological effects, many of these compounds also stimulate the release of norepinephrine from nerve endings. The release of norepinephrine further increases the sympathomimetic effects of these compounds, at least

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use (Refs. 45 and 46). Evidence that ephedrine independently causes an increase in blood pressure when coadministered with caffeine comes from two sources. First, there are studies in which ephedrine and caffeine were tested separately so that their effects could be compared. In a study by Jacobs et al., a group of healthy subjects received ephedrine (E, 0.1 mg/kilogram (kg) orally), caffeine (C, 4 mg/kg orally), the combination, or a placebo (P) (Ref. 49).⁴⁷ SR per SD

Although caffeine caused a small increase in systolic blood pressure (average 3 to 6 mm Hg), ephedrine alone gave a 12 mm Hg effect, and when added to caffeine, increased systolic blood pressure by an additional 15 mm Hg (C+E = 156 +/- 29 mm Hg; E = 150 +/- 14; C = 141 +/- 16; P = 138 +/- 14) (Refs. 47 and 48). Second, ephedrine has been shown in a clinical study to increase blood pressure and heart rate acutely when administered intravenously to children to maintain blood pressure during surgery (Ref. 37). Therefore, these studies show a blood pressure effect from ephedrine itself, independent of any additional effect from caffeine.

In a multiple-dose controlled trial, Boozer et al. (2002) compared the effects of a combination of ephedrine alkaloids (from *Ephedra*) and caffeine (from kola nut) with placebo over a 6-month period in a highly selected population of obese and overweight individuals, who were carefully screened by medical history and medical evaluation to eliminate cardiovascular and other acute or chronic disorders (Ref. 49). The study measured sitting blood pressure in the clinic using the cuff method for all 6 months (at weeks 1, 2, 3, 4, and every 4 weeks thereafter) of the study; these cuff measurements were not taken throughout the day so they reflect only a snapshot of the blood pressure at the time of measurement. The study also measured changes in blood pressure throughout the day at weeks 1, 2 and 4 using an automated

be attributed to the caffeine because the effect of caffeine on blood pressure (discussed previously) is transient, and the acute effect of caffeine to increase blood pressure is lost within 2 weeks of continued use (Refs. 29, 45, and 46). SR for JD

While some effects of sympathomimetics show tachyphylaxis (i.e., decrease in response following repetitive administration of a pharmacologically active substance <http://www.stedmans.com/>) tachyphylaxis usually occurs rapidly. (FDA has verified the Web site address, but FDA is not responsible for any subsequent changes to the nonFDA Web sites after this document publishes in the **Federal Register**.) Therefore, we believe, based upon these data and our experience, that the blood pressure effects of ephedrine alkaloids seen after 4 weeks of continued use will persist. 2-4

The Boozer et al. (2002) study (Ref. 49) was reviewed at our request by three outside scientific experts, Norman M. Kaplan, M.D. (Ref. 50), Richard L. Atkinson, M.D. (Ref. 51), and Mark Espeland, Ph.D. (Ref. 52). These experts were asked to give their independent, scientific opinion of whether the study provides adequate data to assess safety of ephedrine alkaloids and caffeine for weight loss—considering, among other things, the design and duration of the trial and subject selection—and whether further studies are needed. In general, the experts concluded that the safety of ephedrine alkaloid and caffeine containing products could not be established by this study because the study used a highly selected population (i.e., carefully screened by medical history and medical evaluation to eliminate cardiovascular and other acute or chronic disorders) and had relatively few subjects. One of the experts also concluded that the duration of the study was inadequate to establish safety. In general, the reviewers found that the results raised safety concerns. Dr. Kaplan, one of the reviewers, raised the concern that the size of the change in blood

pressure observed with ABPM, when applied to a large population, could translate into a significant increase in the incidence of strokes and heart attacks. Dr. Kaplan's concern reflects the potential consequence of long-term use of ephedra (i.e., the consequence of a population increase in blood pressure). A short-term increase (e.g., 1 to 2 months) would not be expected to have such an effect. Approximately one in four adults has high blood pressure. Of those with high blood pressure, 31 percent are unaware that they have it (Ref. 53). A relative increase in blood pressure in any population, even individuals with "normal" blood pressure, will increase the risk of heart attack, stroke, and death in that population (Refs. 29, 29a, and 54).

The extremely high prevalence of diagnosed and undiagnosed hypertension in the U.S. population and the likelihood that blood pressure in obese patients is already elevated make the 4 mm Hg effect shown by the Boozer et al. (2002) study (Ref. ⁴⁹47) one of great concern. Reductions in blood pressure of this magnitude (i.e., around 4 mm Hg diastolic or systolic) are clearly associated with substantial long-term reductions in the occurrence of heart attack, stroke and death, as seen in meta-analyses of antihypertensive drug trials (Refs. 55 and 56). While these trials were conducted in patients with hypertension, increasing blood pressure in any population, even in individuals with "normal" blood pressure, will increase the risk of cardiovascular disease (Ref. 29). per SP

Epidemiological studies support a graded and continuous relationship between increased blood pressure and risk of stroke, heart attack, and sudden death, even when the increase is within the normal range (i.e., less than 140 mm Hg systolic and less than 90 mm Hg diastolic) (Refs. 29 and 30). This indicates that many people would be at an increased risk with long-term use

in dietary supplements (Ref. 86). Consequently, they recommended removing

dietary supplements containing ephedrine alkaloids from the market (Ref. 87).

Although the CANTOX^{Health Sciences International (CANTOX)} review attempted to establish a level of ephedrine

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alkaloids at which there were no adverse effects, we do not consider the information submitted sufficient to establish a "safe" dose (see discussion of CANTOX in the response to comment 32 of this document).

(Comment 27) Many comments raised the issue of the safety of dietary supplements containing ephedrine alkaloids for use in sensitive or special populations. A number of comments indicated that certain individuals may be relatively more sensitive to the stimulant effects of ephedrine alkaloids, and as a result, at greater risk for adverse health consequences. One comment from a physician noted that he does not recommend the use of ephedra products by pregnant women. Another comment indicated a particular safety concern with the use of dietary supplements containing ephedrine alkaloids in older persons; according to the comment, many elderly persons take medications for which the use of dietary supplements containing ephedrine alkaloids would be contraindicated. Citing a survey that indicated that shift workers frequently use stimulants, including ephedrine alkaloids, in combination with coffee, depressants and/or pain relievers that contain caffeine, one comment expressed the view that ephedrine alkaloids pose a significant health risk to the shift worker population (Ref. 88). The comment further submitted that 69 percent of shift workers are overweight, that shift work is likely to involve physical labor, often performed in hot conditions, and that these factors increase the risks of adverse cardiovascular effects when shift workers use ephedrine alkaloids. Other comments stated that the presence or absence of a susceptible population cannot be determined with the available data. Several comments

chronic use of caffeine has no effect on blood pressure that persists beyond 2 weeks (Refs. 45 and 46), in contrast to ephedrine, which does have a persistent effect (Boozer) (Ref. ⁴⁹47).

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(Comment 31) Many comments contended that we failed to consider the differences among ephedrine alkaloids from the raw botanical; extracts from the raw botanical that contain unaltered proportions of alkaloids and other substances; concentrated and/or otherwise manipulated ephedra extracts such that naturally occurring proportions and/or quantities of ephedrine alkaloids are changed; and synthetic or pure isolated ephedrine (extracted as a single entity from the plant). Because these products have chemical differences and differences in potency, toxicity, pharmacokinetics, and pharmacological and physiological effects, the comments maintained they should be considered separately in scientific, medical, and regulatory contexts.

Other comments, citing a study by White et al., stated that other natural constituents, including other alkaloids and ephedradines in the raw botanical, modify or attenuate the physiological and pharmacological effects of the ephedrine contained in dietary supplements (Ref. 43). Numerous comments maintained that raw *Ephedra* and/or *Ephedra* extracts are safer than ephedrine that is synthetic or that has been isolated and that serious adverse events associated with the appropriate use of ephedra have been rare. Several comments asserted that the ephedradines have hypotensive effects and are found in ephedra roots, rather than the aerial portions of the plant. One comment maintained that ephedradines are thought to occur in small amounts in *Ephedra* stems. One comment stated that ephedra extract is safer than pharmaceutical ephedrine based on the fact that the LD₅₀ is higher for the botanical extract (5.4g/kg) when compared to the LD₅₀ for pharmaceutical

In the case of the Boozer study, the abstract did not provide details on the exclusion or inclusion criteria for the study, so a reader could not determine how the subjects were selected or how they were monitored during the study. The CANTOX authors also did not acknowledge the significance of the blood pressure findings in the Boozer et al. As we have discussed extensively in the ~~the~~ ^{1/2} Pharmacology section V.B.1 of this document, this study by Boozer et al. (Ref. 49) clearly demonstrates a higher blood pressure in ephedra plus caffeine treated subjects (compared to placebo), which translates into serious long-term risks in the general population and serious short-term risks in susceptible populations. Furthermore, as stated by outside scientific experts who reviewed this study, the Boozer et al. (2002) study cannot establish the safety of dietary supplements containing botanical ephedrine alkaloids and caffeine because the study used a highly selected population, had relatively few subjects and was carried out for too short a period of time. Rather, the Boozer study raises questions about the safety of these products.

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Indeed, of the 20 studies that CANTOX considered in identifying the NOAEL, four were abstracts, and two were unpublished reports. Thus, unlike the IOM report's reliance on peer-reviewed journal articles, a significant proportion of the CANTOX "studies" were not subject to peer review.

We also note a number of other deviations from the IOM's application of its risk assessment model (Ref. 28). Compared to the definition in the IOM report, CANTOX expanded the definition of the UL and narrowed the population to which it applies. As noted earlier, the IOM report defined the UL, in part, as "the highest level of daily nutrient intake that is likely to pose no risk of adverse health effects to almost all individuals in the general population." The IOM report stated that the term "tolerable" was chosen

more than 2,200 additional AERs submitted directly to us plus approximately ~~18,000~~ ^{16,000} reports from call records submitted by Metabolife International, one of the largest distributors of dietary supplements containing ephedrine alkaloids. These records have been placed in the record for this rulemaking in redacted form.

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A Congressional subcommittee minority report (Ref. 117), posted at http://www.house.gov/reform/min/pdfs/pdf_inves/pdf_dietary_ephedra_metabolife_rep.pdf⁴ noted that the call records from Metabolife International contain nearly 2,000 reports of significant AERs for its products, including 3 deaths, 20 heart attacks, 24 strokes, 40 seizures, 465 episodes of chest pain, and 966 reports of heart rhythm disturbances. In addition to these cardiac and neurological events, psychiatric symptoms were also reported. These reports include 46 reports of hospitalization following use of their products, and 82 additional reports of emergency room care. The report stated that in more than 90 percent of the most serious AERs— stroke, heart attack, seizure, and psychosis—where dosage information is documented in the call record, the consumer had followed the manufacturer’s dosage recommendations. It also stated that among those most significant adverse event reports for which age was noted, 50 percent of the consumers were under 35 and many of the consumers were reported as being in good health with no prior medical problems. Despite the limited information provided in Metabolife International’s call records, we note that these types of adverse events reported are consistent with the scientifically documented effects and potential risks of ephedrine alkaloids in those cases where appropriate information was available to make a medical evaluation of the reported event.

⁴ FDA has verified the Web site address, but FDA is not responsible for any subsequent changes to the nonFDA Web sites after this document publishes in the **Federal Register**.

NEWS/ephedra/letterslist.html (list of firms) and *http://www.fda.gov/bbs/topics/NEWS/ephedra/warning.html* (sample letter).

3. Eased Breathing

We are aware that there are teas and other types of dietary supplements containing ephedrine alkaloids marketed with claims such as “eased breathing” or “better breathing.” ~~We are not aware, however, of any reasonably likely benefit from the use of these products.~~ There are no data that support a benefit to breathing from dietary supplements containing ephedrine alkaloids in healthy people. Moreover, because healthy people are able to breathe without difficulty, we do not believe there is any respiratory benefit in the absence of a disease state (e.g., asthma or a respiratory infection). We note that claims to treat or mitigate a disease, or the effects of a disease, subject a product to regulation as a drug under the act.

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4. Other Uses

We are also aware that dietary supplements containing ephedrine alkaloids are promoted for other uses, such as to “feel better,” “feel more alert,” and “energized.” Effects such as “feel better” are subjective in nature and difficult to quantify. The agency is unaware of any data substantiating these types of subjective effects. Effects such as “alertness” and “energy” are consistent with the pharmacological properties of ephedrine alkaloids, although we are not aware of any studies evaluating ephedrine alkaloid products for these uses. Effects like alertness and energy may be of modest benefit to the individual (if they occur), but such effects are temporary and do not improve health. Any such temporary benefits must be weighed against the health risks discussed in section V.B of this document, which can result in long-term or permanent, serious adverse health effects.

2. Do Dietary Supplements Containing Ephedrine Alkaloids Present an Unreasonable Risk Under Labeled or Ordinary Conditions of Use?

(Comment 63) Several comments stated there is enough evidence, both scientific and anecdotal, to conclude that the risks of taking dietary supplements containing ephedrine alkaloids are so severe and reported adverse events sufficiently numerous to conclude that the risks clearly exceed the benefits because either there are no benefits or the benefits are unsubstantiated or modest for both efficacy and duration. These comments included references to support their conclusions. Some cited the RAND report's conclusions regarding the very modest benefit for short-term weight loss and the questionable benefit for other uses; according to the comments, these limited or questionable benefits are far outweighed by adverse events observed in clinical trials. Other references submitted by these comments included (Refs. 19, 34, 42, ^{and through} ~~133, 134, 135, 136, and 137~~).

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Several comments argued that the harm caused by certain medical conditions—for example, obesity—is so severe as to render the unsubstantiated (in the commenter's view) risks of taking dietary supplements containing ephedrine alkaloids insignificant relative to the benefits that would accrue from use of these products. In this view, the weight loss benefit would exceed any potential risk from taking the product and the risk is not unreasonable when compared to the harm caused by obesity. Several comments cited the prevalence of obesity and an increase in obesity over time, and urged us not to take away one important tool for consumers to address the problem. Two comments cited statistics showing that 54 percent of adults are obese in the United States, that the prevalence of obesity increased by 30 percent from 1980 to 1994, and that in 1997 the Centers for Disease Control and Prevention (CDC)

adverse events reported to us); instructed the Committee to evaluate safety using an interpretation of “significant harm” (i.e., either a large number of adverse events or a serious adverse event in one individual) that is not specified in DSHEA; and improperly asked the Committee to recommend action to reduce the risks associated with the use of these products.

Other comments argued that the procedures we followed at the Committees’ meetings were unfair. The comments cited several reasons, including the following: FDA materials were not made available to dietary supplement industry groups and other interested persons prior to the meetings; we were given unlimited time to “influence” the Committee, and the time others were given to present comments was limited; and interested persons were not allowed to question FDA officials. For these reasons, several of these comments stated that we must reconvene the Committee.

(Response) We disagree with the comments. The comments concerning the data and information we presented or did not present during the meetings are without merit because the essence of these comments is that they disagreed with our interpretation of the data or preliminary conclusions. Presenting our interpretation of the data and our preliminary conclusions is entirely appropriate and does not constitute undue influence over the Committees (Ref. ¹³⁷~~138~~). Interested persons, including the dietary supplement industry, were provided with ample opportunity to express their views and present data they believed relevant to the evaluation during the public hearing portions of the meetings or in written comments to the Committees. To the extent that specific comments on the data, our interpretation of the data, and our preliminary conclusions are relevant to this rulemaking, they are addressed in other sections of this document.

Regarding the conduct of the Committees' meetings, those meetings were conducted in accordance with the Federal Advisory Committee Act (5 U.S.C. App. 2), FDA's implementing regulations (21 CFR part 14), and FDA guidance entitled "Policy and Guidance Handbook for FDA Advisory Committees" (1994) (Ref. ¹³⁷~~138~~). We also note that the procedures followed during these meetings were no different from the procedures used in conducting the numerous advisory committee meetings we have held on a variety of other issues.

We convened the Committees as a means to acquire independent scientific and technical advice on the public health concerns surrounding the use of dietary supplements containing ephedrine alkaloids and on specific ways to address these public health concerns. During the meetings, we implemented several safeguards to ensure the Committees' independence and fairness to all interested parties.

First, it was made entirely clear during the meetings that the Committees' members were invited to express a view different than ours, so that our tentative conclusions could be revised, if necessary. During these meetings, we presented a critical and fair evaluation and interpretation of the available data. We also expressed our tentative conclusions and our concern for the public health. Again, it is entirely appropriate for us to state our views and interpretation of the data. Furthermore, individual members of the Committees took advantage of the many opportunities during the meetings to discuss their views and to question FDA officials about the available data, our interpretation of the data, and our tentative position.

Second, the Committees included consumer and industry representatives, including two representatives from associations representing the dietary

It is important to note that the AERs are not the principal scientific basis for the regulatory action we selected. Instead, the AERs are consistent with the known pharmacological and physiological effects of ephedrine alkaloids, as well as the results of clinical studies and, therefore, support our finding of unreasonable risk. As we explain in more detail later in this document, we use a high barrier before admitting an AER as evidence of adverse events associated with ephedrine alkaloids. We also use conservative methods to infer the total number of adverse events from the reports.

i. *Use of AERs in ~~Estimating Benefits and Baseline~~ Number of AERs.* In the analysis of the June 1997 proposal, we based our estimate of the impact of removing dietary supplements containing ephedrine alkaloids from the market on the estimated annual number of adverse events caused by dietary supplements containing ephedrine alkaloids (62 FR 30678 at 30705). We based the latter estimate on the average annual number of AERs that we received between January 1993 and June 1996, that we suspected of having been caused by these supplements, which we characterized as the “baseline number of AERs.” We then adjusted this number of AERs by a series of assumptions designed to reflect various sources of uncertainty over whether these supplements actually caused those AERs and the uncertainty over the relationship between the AERs and the actual number of adverse events associated with the use of dietary supplements containing ephedrine alkaloids (including both reported and unreported adverse events).

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(Comment 73) A number of comments on the June 1997 proposal addressed the issue of the baseline number of AERs. Some comments objected to adjusting the number of AERs with assumptions designed to reflect uncertainty over the relevance of those AERs. One comment said we should

Some comments criticized the report that RAND prepared for HHS on the safety and effectiveness of dietary supplements containing ephedrine alkaloids because of its attention to AERs (Ref. 22). One comment argued that RAND's approach was inappropriate because GAO had previously criticized our use of the AERs in the analysis of the June 1997 proposal. Other comments supported RAND's attention to AERs. One comment argued that RAND did not adequately account for preexisting health conditions when classifying events in the AERs as "sentinel" or "possibly sentinel" events. Other comments criticized RAND's review of the clinical studies involving ephedrine alkaloids. One comment argued that the method RAND used to determine which clinical studies to review was biased. Some comments argued that the results of RAND's review of the AERs were inconsistent with the results of RAND's review of the clinical studies because the clinical studies enrolled enough patients to uncover the types of adverse events that appear in the AERs, if ephedrine alkaloids could cause those types of events. Other comments suggested that sources other than the RAND report provide better assessments of the risks associated with dietary supplements containing ephedrine alkaloids.

Other comments addressed one or more of the other articles that we listed in the March 2003 reopening of the comment period. Many comments criticized one or more of those studies on various bases. Other comments supported one or more of those studies. One comment argued that we presented a biased list of studies because we ignored four other articles that were published at about the same time as the articles that we listed. Some comments noted that RAND said that clinical trials that they reviewed had

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we assumed a 50 percent reporting rate in our report on Eosinophilia-Myalgia Syndrome, which was an outbreak level event (Ref. ~~130~~¹³⁸). These comments noted that this report referred to adverse events related to a dietary supplement, L-tryptophan, which had also received significant media publicity. These comments argued that it was, therefore, a reasonable model to use for the ephedrine alkaloid situation. Some comments suggested that we revise our reporting rate assumption from 10 percent to a range of 10 percent to 50 percent.

Other comments argued that our assumption of a 10 percent reporting rate was too high. Some comments argued that people are more likely to underreport than overreport adverse events involving dietary supplements containing ephedrine alkaloids for various reasons, such as not wanting to acknowledge using the product. One comment noted that a 2001 report from the Office of the Inspector General of HHS concluded that current surveillance systems for identifying adverse reactions from dietary supplements probably detect less than 1 percent of adverse reactions (Ref. 20). However, another comment claimed that most researchers consider a reporting rate of less than 1 percent to reflect a worst-case scenario. One comment noted that the report that suggested a reporting rate of less than 1 percent did not differentiate between serious and nonserious adverse events. This comment argued that the reporting rate for serious adverse events is probably higher than for nonserious adverse events.

(Response) In order to express the continuing uncertainty over the reporting rate, we have calculated benefits based on reporting rates of 10 percent, 50 percent, and 100 percent of sentinel and possible sentinel events. Although the reporting rate could be lower than 10 percent, the severity of

TABLE 8.—SUMMARY OF OPTIONS, ROUNDED TO \$ MILLIONS—Continued

Option	Annual Cost	Annual Benefit	Net
3. Require 2003 warning statement	\$0 to \$1	\$0 to \$20	-\$1 to \$20
4. Require warning statement, but modify it or require only on certain products	NA	NA	NA
5. Generate additional information or take some action other than removal or warning statements	unknown	unknown	unknown

B. Small Entity Analysis

We have examined the economic implications of this final rule as required by the Regulatory Flexibility Act (5 U.S.C. 601–612) and in accordance with Executive Order 13272 (August 13, 2002). If a rule has a significant economic impact on a substantial number of small entities, the Regulatory Flexibility Act requires us to analyze regulatory options that would lessen the economic effect of the rule on small entities. We find that this final rule would have a significant economic impact on a substantial number of small entities.

(Comment 99) Some comments addressed our estimate of the number of small firms in the analysis of the proposed rule. Some comments argued that we had ignored a large number of independent small distributors in the analysis of the proposed rule. One comment suggested we revisit our analysis of the impact of the rule on small businesses. One comment suggested we obtain information on the impact of the rule on small entities by opening a dialogue with industry associations.

(Response) We have revisited and revised our estimate of the number of firms based on a database of dietary supplement products that the Research Triangle Institute compiled under contract to FDA after publication of the proposed rule. This database listed 30 firms associated with 48 dietary supplement products containing ephedrine alkaloids (Ref. ¹⁵⁹~~158~~). To estimate the number of these firms that are small, we used a database of dietary supplement manufacturing practices that was also compiled by RTI under

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and Independent Regulatory Agencies, dated October 28, 1999) (Ref. 161).

Thus, we certify that the intergovernmental consultation process described in section 4(d) of Executive Order 13132 did not occur for the proposed rule, but we also believe that State and local governments had sufficient notice and an opportunity to participate in this rulemaking process. We note that the proposed rule was subject to a previous Executive Order, Executive Order 12612, which was also entitled, "Federalism," and had a similar consultation and notification obligation for federal agencies. When we issued the proposed rule, we notified the States, and State and local health departments, among others, submitted comments to the proposal (65 FR 17474, April 3, 2000) (stating that State and local health departments and government agencies had commented on the proposed rule)). Furthermore, a subsequent notice, published on March 5, 2003, expressly asked whether we should determine that dietary supplements containing ephedrine alkaloids present a "significant or unreasonable risk of illness or injury" under section 402(f)(1)(A) of the act (68 FR at 10417, 10419, and 10420). Although the March 2003 notice did not contain a separate Federalism analysis, we believe that States were aware of the March 2003 notice because at least five State or local governments or legislators submitted comments in response to the March 2003 notice, and most of these comments urged us to ban the sale of such products.

XII. References

The following references have been placed on display in the Division of Dockets Management (see **ADDRESSES**) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday. (FDA has verified the Web site addresses, but FDA is not responsible for any subsequent changes to the nonFDA Web sites after this document publishes in the **Federal Register**.)

1. Ephedra Monograph, Review of Natural Products, Der Marderosian, A., Ed., DrugFacts.com (<http://www.factsandcomparisons.com>) 2003. pen 2/3
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2. Chen, K. K. and C. F. Schmidt, "Ephedrine and Related Substances," *Medicine* 9:1-117, 1930.
3. Mahuang (Appendix: Mahuanggen), Chapter in Chang, H-M. and P. P-H. But, Eds., *Pharmacology and Applications of Chinese Materia Medica*, pp. 1119-1124, Singapore: World Scientific Publishing Co. Pte. Ltd., pp. 1119-1124, 1987. x
4. Karch, S. B., "Other Naturally Occurring Stimulants," Chapter in Karch, S. B., *The Pathology of Drug Abuse*, pp. 177-198, Boca Raton: CRC Press, 1996.
5. "Phenethylamines," Chapter in Bruneton, J., ed., *Pharmacognosy, Phytochemistry, Medicinal Plants*, pp. 711-715, New York: Laviosier Publishing, 1995.
6. Betz, J. M., Tab F, "Review of Plant Chemistry: Alkaloids of Ma Huang (ephedra spp.)," Food and Drug Administration, Briefing Materials for Food Advisory Committee Special Working Group on Foods Containing Ephedrine Alkaloids, Center for Food Safety and Applied Nutrition, pp. 1-14, 1995.
7. World Health Organization (WHO) Monographs on Selected Medicinal Plants, *Herba Ephedrae*, pp. 145-153, 1999.
8. Oshio, H., M. Tsukui, and T. Matsuoka, "Isolation of *l*-Ephedrine From 'Pinelliae Tuber'" *Chemical and Pharmaceutical Bulletin* (Tokyo), vol. 26, pp. 2096-2097, 1978. ✓
9. Ghosal, S., R. B. Chauhan, and R. Mehta, "Alkaloids of Sida Cordifolia," Phytochemical Reports, vol. 14, pp. 830-832, 1975. chemical/subst
10. Cui, J., T. Zhou, J. Zhang, and Z. Lou, "Analysis of Alkaloids in Chinese Ephedra Species by Gas Chromatographic Methods," *Phytochemical Analysis*, vol. 2, pp. 116-119, 1991.
11. Food and Drug Administration, Tab E: Additional Market Review Information. Briefing Materials for Food Advisory Committee on Dietary Supplements

21. Shekelle P., S. Morton, M Maglione, et al., "Ephedra and Ephedrine for Weight Loss and Athletic Performance Enhancement: Clinical Efficacy and Side Effects. Evidence Report/Technology Assessment," No. 76 (Prepared by Southern California Evidence-based Practice Center, RAND, under Contract No. 290-97-0001, Task Order No. 9), AHRQ Publication No. 03-E022, Rockville, MD, Agency for Healthcare Research and Quality, Docket No. 1995N-0304, BKG3, vol. 300 (<http://www.fda.gov/OHRMS/DOCKETS/98fr/95n-0304-bkg0003-ref-07-01-index.htm>), 2003.

22. Shekelle, P. G., M. L. Hardy, S. C. Morton, et al., "Efficacy and Safety of Ephedra and Ephedrine for Weight Loss and Athletic Performance: A Meta-Analysis," *Journal of the American Medical Association*, vol. 289, pp. 1537-1545, 2003.

23. U.S. General Accounting Office (GAO), "Dietary Supplements Containing Ephedra, Health Risks and FDA's Oversight," Testimony: Before the Subcommittee on Oversight and Investigations, Committee on Energy and Commerce, U.S. House of Representatives, GAO-03-1042T, 2003.

24. U.S. General Accounting Office (GAO): "Dietary Supplements: Review of Health-Related Call Records for Users of Metabolife 356," GAO-03-494, 2003.

25. Caveney, S. and A. Starratt, "Glutamatergic Signals in Ephedra (Scientific Correspondence)," *Lancet*, vol. 372, p. 509, 1994.

26. Caveney, S., D. A. Charlet, H. Freitag, et al., "New Observations on the Secondary Chemistry of World *Ephedra* (Ephedraceae)," *American Journal of Botany*, vol. 88, pp. 1199-1208, 2001.

27. Food and Drug Administration, L. A. Love, Tab E, "Evaluation of the Safety of Food Products Containing Sources of Ephedrine Alkaloids," Briefing Materials for Food Advisory Committee Special Working Group on Foods Containing Ephedrine Alkaloids, Center for Food Safety and Applied Nutrition, pp. 1-51, 1995.

28. Food and Nutrition Board, Institute of Medicine, Dietary Reference Intakes: A Risk Assessment Model for Establishing Upper Intake Levels for Nutrients, Washington DC, National Academy Press, pp. 1–71, 1999.

29. Vasan, R. S., M. G. Larson, E. P. Leip, et al., “Impact of High-Normal Blood Pressure on the Risk of Cardiovascular Disease,” *New England Journal of Medicine*, vol. 345, pp. 1291–1297, 2001.

29a. Vasan, R. S., J. M. Massaro, P. W. Wilson, et al., “Antecedent Blood Pressure and Risk of Cardiovascular Disease: The Framingham Heart Study,” *Circulation*, vol. 105, pp. 48–53, 2002.

30. Neaton, J. D., L. Kuller, J. Stamler, and D. N. Wentworth, Impact of systolic and diastolic blood pressure on cardiovascular mortality, Chapter in Laragh, J. H. and B. M. and Brenner, eds., *Hypertension: Pathophysiology, Diagnosis, and Management*, New York: Raven Press Ltd., pp. 127–144, 1995.

31. National Institutes of Health (NIH), Report of Ephedra Working Group to the National Advisory Council for Complementary and Alternative Medicine (<http://nccam.nih.gov/health/alerts/ephedra/working-group.htm>), 2003.

32. Goldman, S. A., D. L. Kennedy, D. J. Graham, et al., “The Clinical Impact of Adverse Event Reporting,” *MedWatch Continuing Education Article*, pp. 1–11, 1996.

33. Middleton, W. S. and K. K. Chen, “Ephedrine,” *Archives of Internal Medicine*, vol. 39, pp. 385–403, 1927.

34. Haller, C. A. and N. L. Benowitz, “Adverse Cardiovascular and Central Nervous System Events Associated With Dietary Supplements Containing Ephedra Alkaloids,” *New England Journal of Medicine*, vol. 343, pp. 1833–1838, 2000.

35. Hoffman, B. B. and R. J. Lefkowitz, “Catecholamines, Sympathomimetic Drugs, and Adrenergic Receptor Antagonists,” Chapter in Hardman, J. G., A. G. Gilman, and L. E. Limbird, eds., *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, New York, St. Louis, McGraw-Hill Chapter, pp. 199–248, 1996.

36. Astrup, A., S. Toubro, S. Cannon, et al., "Thermogenic Synergism Between Ephedrine and Caffeine in Healthy Volunteers: A Double-Blind, Placebo-Controlled Study," *Metabolism*, vol. 40, pp. 323–329, 1991.
37. Taguchi, N., T. Nishikawa, S. Inomata, et al., "Hemodynamic Effects of Intravenous Ephedrine in Infants and Children Anesthetized With Halothane and Nitrous Oxide," *Anesthesia and Analgesia*, vol. 82, pp. 568–573, 1996.
38. The Xamoterol in Severe Heart Failure Study Group, "Xamoterol in Severe Heart Failure," *Lancet*, vol. 336, pp. 1–6, 1990.
39. Packer, M., J. R. Carver, R. J. Rodeheffer, et al., "Effect of Oral Milrinone on Mortality in Severe Chronic Heart Failure, The PROMISE Study Research Group," *New England Journal of Medicine*, vol. 325, pp. 1468–1475, 1991.
40. Cowley, A. J. and A. M. Skene, "Treatment of Severe Heart Failure: Quantity or Quality of Life? A Trial of Enoximone," Enoximone Investigators, *British Heart Journal*, vol. 72, pp. 226–230, 1994.
41. Brown, O. M. Adrenergic Drugs, Chapter in Smith, C. M. and A. M. Reynard, eds., *Essentials of Pharmacology*, Philadelphia, W. B. Saunders Co., pp. 75–85, 1995.
42. Haller, C. A., P. Jacob, III and N. L. Benowitz, "Pharmacology of Ephedra Alkaloids and Caffeine After Single-Dose Dietary Supplement Use," *Clinical Pharmacology and Therapeutics*, vol. 71, pp. 421–432, 2002.
43. White, L. M., S. F. Gardner, B. J. Gurley, et al., "Pharmacokinetics and Cardiovascular Effects of Ma-huang (Ephedra Sinica) in Normotensive Adults," *Journal Clinical Pharmacology*, vol. 37, pp. 116–122, 1997.
44. Gurley, B. J., S. F. Gardner, L. M. White, et al., "Ephedrine Pharmacokinetics After the Ingestion of Nutritional Supplements Containing Ephedra Sinica (Ma Huang)," *Therapeutic Drug Monitoring*, vol. 20, pp. 439–445, 1998.
45. Eggertsen, R., A. Andreasson, T. Hedner, et al., "Effect of Coffee on Ambulatory Blood Pressure in Patients With Treated Hypertension," *Journal of Internal Medicine*, vol. 233, pp. 351–355, 1993.

62. Sears, M. R., "Adverse Effects of Aeta-Agonists," *Journal of Allergy and Clinical Immunology*, vol. 110, pp. S322–S328, 2002.
63. Wit, A. L., B. F. Hoffman, and M. R. Rosen, "Electrophysiology and Pharmacology of Cardiac Arrhythmias, IX. Cardiac Electrophysiologic Effects of Beta Adrenergic Receptor Stimulation and Blockade. Part C," *American Heart Journal*, vol. 90, pp. 795–803, 1975.
64. Mahaffey, K. W., J. A. Puma, N. A. Barbagelata, et al., "Adenosine as an Adjunct to Thrombolytic Therapy for Acute Myocardial Infarction: Results of a Multicenter, Randomized, Placebo-Controlled Trial: The Acute Myocardial Infarction Study of Adenosine (AMISTAD) Trial," *Journal of the American College of Cardiology*, vol. 34, pp. 1711–1720, 1999.
65. Kenchaiah, S., J. C. Evans, D. Levy, et al., "Obesity and the Risk of Heart Failure," *New England Journal of Medicine*, vol. 347, pp. 305–313, 2002.
66. National Institutes of Health, National Heart, Lung, and Blood Institute, "Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults: The Evidence Report," NIH Publication No. 98-4083 (http://www.nhlbi.nih.gov/guidelines/obesity/ob_gdlns.htm), 1998. pp. 1-262
see JD markups
67. Astrup, A., L. Breum, S. Toubro, et al., "The Effect and Safety of an Ephedrine/Caffeine Compound Compared to Ephedrine, Caffeine and Placebo in Obese Subjects on an Energy Restricted Diet, A Double Blind Trial," *International Journal of Obesity and Related Metabolic Disorders*, vol. 16, pp. 269–277, 1992.
68. Toubro, S., A. V. Astrup, L. Breu, F. Quaade, "Safety and Efficacy of Long-Term Treatment With Ephedrine, Caffeine and an Ephedrine/Caffeine Mixture," *International Journal of Obesity and Related Metabolic Disorders*, vol. 17, suppl. 1, pp. S69–S72, 1993.
69. Quaade, F., A. Astrup, L. Breum, ^{et al.} ~~S. Toubro, P. Hein,~~ "The effect of an Ephedrine/Caffeine Combination As a Supplement to a Weight-Reducing Diet." A ✓

Randomized, Placebo-Controlled, Double-Blind Trial," *Ugesk Laeger*, vol. 154, pp. 1258–1263, 1992.

70. Toubro, S., A. Astrup, L. Breum, et al., "The Acute and Chronic Effects of Ephedrine/Caffeine Mixtures on Energy Expenditure and Glucose Metabolism in Humans," *International Journal of Obesity and Related Metabolic Disorders*, vol. 17, suppl. 3, pp. S73–S77, 1993.

71. Astrup, A., C. Lundsgaard, J. Madsen, et al., "Enhanced Thermogenic Responsiveness During Chronic Ephedrine Treatment in Man," *American Journal Clinical Nutrition*, vol. 42, pp. 83–94, 1985.

72. Astrup, A. and S. Toubro, "Thermogenic, Metabolic, and Cardiovascular Responses to Ephedrine and Caffeine in Man," *International Journal of Obesity and Related Metabolic Disorders*, vol. 17, suppl. 1, pp. S41–S43, 1993.

73. Astrup, A., S. Toubro, S. Cannon, P. Hein, et al., "Caffeine: A Double-Blind, Placebo-Controlled Study of its Thermogenic, Metabolic, and Cardiovascular Effects in Healthy Volunteers," *American Journal Clinical Nutrition*, vol. 51, pp. 759–767, 1990.

74. Breum, L., J. K. Pedersen, F. Ahlstrom, et al., "Comparison of an Ephedrine/Caffeine Combination and Dexfenfluramine in the Treatment of Obesity. A Double-Blind Multi-Centre Trial in Ggeneral Practice," *International Journal of Obesity and Related Metabolic Disorders*, vol. 18, pp. 99–103, 1994.

75. Pasquali, R., G. Baraldi, M. P. Cesari, et al., "A Controlled Trial Using Ephedrine in the Treatment of Obesity," *International Journal of Obesity and Related Metabolic Disorders*, vol. 9, pp. 93–98, 1985.

76. Pasquali, R., M. P. Cesari, N. Melchionda, et al., "Does Ephedrine Promote Weight Loss in Low-Energy-Adapted Obese Women?," *International Journal of Obesity and Related Metabolic Disorders*, vol. 11, pp. 163–168, 1987.

77. Pasquali, R., F. Casimirri, N. Melchionda, et al., "Effects of Chronic Administration of Ephedrine During Very-Low-Calorie Diets on Energy Expenditure,

Protein Metabolism and Hormone Levels in Obese Subjects," *Clinical Science* (London), vol. 82, pp. 85–92, 1992.

78. Krieger, D. R., Daly, P. A., Dulloo, A. G., et al., "Ephedrine, Caffeine and Aspirin Promote Weight Loss in Obese Subjects," *Transactions of the Association of American Physicians*, vol. 103, pp. 307–312, 1990.

79. Daly, P. A., D. R. Krieger, A. G. Dulloo, et al., "Ephedrine, Caffeine and Aspirin: Safety and Efficacy for Treatment of Human Obesity," *International Journal of Obesity and Related Metabolic Disorders*, vol. 17, suppl. 1, pp. S73–S78, 1993.

80. Horton, T. J. and C. A. Geissler, "Aspirin Potentiates the Effect of Ephedrine on the Thermogenic Response to a Meal in Obese But Not Lean Women," *International Journal of Obesity and Related Metabolic Disorders*, vol. 15, pp. 359–366, 1991.

80a. Food and Drug Administration, Memorandum, Beaton, P., M.D., Ph.D., "Review of Boozer-Daly Article for Ephedrine and Caffeine," January 10, 2003, amended February 2, 2004.

81. Food and Drug Administration, Memorandum: Evaluation of Scientific References Considered by RAND, February 2, 2004.

81a. Friedman, L. M., C. D. Furberg, and D. L. DeMets, *Fundamentals of Clinical Trials*, 3rd ed., Springer, New York, 1998.

81b. Ingelfinger, J.A., F. Mosteller, L. A. Thibodeau, et al., 3rd ed., *Biostatistics in Clinical Medicine*, McGraw-Hill, Inc., New York, 1994.

81c. Dawson, B. and R.G. Trapp, *Basic and Clinical Biostatistics*, 3rd ed., Lange Medical Books/McGraw-Hill, New York, 2001.

82. Niemann R.A. and M.L. Gay, "Determination of Ephedrine Alkaloids and Synephrine in Dietary Supplements by Column-Switching Cation Exchange High-Performance Liquid Chromatography with Scanning-Wavelength Ultraviolet and Fluorescence Detection," *Journal of Agricultural and Food Chemistry*, vol. 51, pp. 5630–5638, 2003.

83. Chua, S. S. and S. I. Benrimoj, "Non-Prescription Sympathomimetic Agents and Hypertension," *Medical Toxicology and Adverse Drug Experience*, vol. 3, pp. 387-417, 1988.
84. Inchiosa, M. A., "Dose-Related Cardiovascular Effects of Ephedrine in Humans," Report prepared for the Food and Drug Administration, July 6, 1999.
85. Inchiosa, M. A., "Bioavailability of Ephedrine Alkaloids," Report prepared for the Food and Drug Administration, June 14, 1999.
86. Food and Drug Administration, Food Advisory Committee on Dietary Supplements Containing Ephedrine Alkaloids, Meeting Transcript, II, pp. 136, 137, 203, 205, 221, 225, 227, 229-²30, 236-²37, 239-²40, August 27-28, 1996. sorry ✓
87. Food and Drug Administration, Food Advisory Committee on Dietary Supplements Containing Ephedrine Alkaloids, Meeting Transcript, II, pp. 137, 233, 237, 240, 272, and 277, August 27-28, 1996.
88. Kerin, K. J., Dietary Supplements Containing Ephedrine Alkaloids, Comments from Circadian Technologies, Inc., FDA Docket No. ¹⁹95N-0304, c3923:1-3, 2003. ✓
89. Lee, M. K., B. W. Cheng, C. T. Che, et al., "Cytotoxicity Assessment of Ma-huang (Ephedra) Under Different Conditions of Preparation," *Toxicological Sciences*, vol. 56, pp. 424-430, 2000.
90. Hikino, H., K. Ogata, C. Konno, et al., "Hypotensive Actions of Ephedradines, Macrocylic Spermine Alkaloids of Ephedra Roots," *Planta Medica*, vol. 48, pp. 290-293, 1983.
91. Minematsu, S., Y. Kobayashi, N. Kobayashi, ~~Y. Fujii~~² et al., "Acute Ephedrae Herba and ephedrine poisoning in mice," *Japanese Journal of Toxicology*, vol. 4, pp. 143-149, 1991.
92. Lee, M. K., Y. H. Wong, C. T. Che, et al., "Adrenergic Agonistic Effects and Cyto-Toxicity of Chinese Ephedra (Ma-Huang) Used for Weight Reduction," *Toxicological Sciences, The Toxicologist*, vol. 48:58, p. 272, 1999.

93. CANTOX Health Sciences International, "Safety Assessment and Determination of a Tolerable Upper Limit for Ephedra," ^{pp.} 1-273, Docket No. 2000N-1200, Sup2 (<http://www.crnusa.org/cantoxreportindex.html>), 2000. ✓
94. Ad Hoc Committee Reports, On the Safety of Ma Huang (1995, 1996), On the Safety of Dietary Supplements (1997), FDA Docket Nos. 1995N-0304, RPT 1, vol. ^s 36-38; 1995N-0304, C57, vol. 76; 1995N-0304, C3391, vol. 280. ✓
95. Ephedra Education Council Expert Panel Report, Docket No. 2000N-1200, C30, vol. 70, 2000.
96. Boozer, C. N., P. A. Daly, D. Blanchard, et al., "Herbal Ephedra/Caffeine for Weight Loss: A 6-Month Safety and Efficacy Trial," *North American Association for the Study of Obesity*, 2000. ✓
97. Dulfano, M. J. and P. Glass, "Evaluation of a New B₂ Adrenergic Receptor Stimulant, Terbutaline, in Bronchial Asthma. II. Oral Comparison With Ephedrine," *Current Therapeutic Research*, vol. 15, pp. 150-157, 1973. ✓
98. Tashkin, D. P., R. Meth, D. H. ~~Simmons~~ [#], and ~~Y. E. Lee~~ ^{et al.}, "Double-Blind Comparison of Acute Bronchial and Cardiovascular Effects of Oral Terbutaline and Ephedrine," *Chest*, vol. 68, pp. 155-161, 1975. ✓
99. Brown, S. D., Jr. [#] and F. J. Landry, "Recognizing, Reporting, and Reducing Adverse Drug Reactions," *Southern Medical Journal*, vol. 94, pp. 370-373, 2001.
100. Lazarou, J., B. H. Pomeranz, and P. N. Corey, "Incidence of Adverse Drug Reactions in Hospitalized Patients: A Meta-Analysis of Prospective Studies," *Journal of the American Medical Association*, vol. 279, pp. 1200-1205, 1998.
101. American Herbal Products Association, *Code of Ethics and Business Conduct*, pp. 1-9, July 2002.
102. Lake, C. R. and R. S. Quirk, "CNS Stimulants and the Look-Alike Drugs," *Psychiatric Clinics of North America*, vol. 7, pp. 689-701, 1984. ✓

103. Furuya, I. and S. Watanabe, "Discriminative Stimulus Properties of Ephedra Herb (*Ephedra Sinica*) in Rats," *Yakubutsu Seishin Kodo* (Japanese Journal of Psychopharmacology), vol. 13, pp. 33–38, 1993.

104. Tinsley, J. A. and D. D. Watkins, "Over-the-Counter Stimulants: Abuse and Addiction," *Mayo Clinic Proceedings*, vol. 73, pp. 977–982, 1998.

105. Ephedra Sinica, In Gruenwald, J., T. Brendler, and C. Jaenicke, eds., *PDR for Herbal Medicines*, 1st ed., Montvale: Medical Economics Co., Inc., pp. 826–827, 1998.

106. The Complete German Commission E Monographs, Therapeutic Guide to Herbal Medicines (English Translation), Blumenthal, M., W. R. Busse, A. Goldberg, et al. ✓
~~J. Gruenwald, T. Hall, C. W. Riggins, and R. S. Rister~~, pp. 125–126, 1998.

107. Huang, K. C., Antiasthmatic herbs, Chapter in *The Pharmacology of Chinese Herbs*, pp. 229–232, Boca Raton, CRC Press, 1993.

108. Hsu, H. Y., Y. P. Chen, S. J. Shen, et al. #
 Ephedrae Herba (*Ephedra*, Ma-Huang), *Oriental Materia Medica: A Concise Guide*, pp. 52–53, Long Beach, CA, Oriental Healing Arts Institute, 1986.

109. Food and Drug Administration, Clinical Research and Review Staff: Evaluation of Adverse Events Reported With the Use of Ephedrine Alkaloid-containing Dietary Supplements (June 1, 1997, through March 31, 1999), 2000.

110. Food and Drug Administration, Chen, M. and C. B. Karwoski, Office of Post Market Drug Risk Assessment Postmarketing Safety Review, "Evaluation of Adverse Event Reports Associated With Ephedrine Alkaloid-Containing Dietary Supplements," 2000.

111. Woosley, R. L., "Summary of Analysis of Adverse Event Reports for Dietary Supplements Containing Ephedrine Alkaloids," Report Prepared for the Food and Drug Administration, 1999.

112. Benowitz, N. L., "Review of Adverse Reaction Reports Involving Ephedrine-Containing Herbal Products," Report Prepared for the Food and Drug Administration, 2000.

113. Ricaurte, G. A., "Review of FDA Neuropsychiatric/central nervous system adverse events related to ephedrine-containing dietary supplements," Report Prepared for the Food and Drug Administration, 2000.

114. Stoll, A. L., "FDA Ephedrine Adverse Event Case Review: Summary," 1999.

115. Woosley, R. L., "FDA Addendum: Summary of Analysis of Adverse Event Reports for Dietary Supplements Containing Ephedrine Alkaloids," Report Prepared for the Food and Drug Administration, 2000.

116. Food and Drug Administration, Love, L. A., "FDA Review of the Published Literature on the Physiological, Pharmacological and Toxic Effects of Ephedrine Alkaloids," 2000.

117. U.S. House of Representatives, Committee on Government Reform, Minority Staff Report, "Adverse Event Reports from Metabolife," 2002.

118. Shekelle, P. G., E-Mail Response to Questions on the RAND Report on Ephedra, April 7, 2003.

119. Shekelle, P. G., M. Maglione, and S. C. Morton, "Preponderance of Evidence. Judging What to Do About Ephedra," RAND Review, vol. 27, pp. 16–21, (<http://www.rand.org/publications/randreview/issues/spring2003/evidence.html>), 2003, accessed in January 2004.

120. "Danish Medicines Agency: Letigenr has been suspended," Danish Medicines Agency 2002 (http://www.laegemiddelstyrelsen.dk/en/news/letigen_6_en.asp), accessed as of March 3, 2003. (To obtain a paper copy see the **FOR FURTHER INFORMATION CONTACT** section of this document.)

121. "Adverse Reactions Letigen," Danish Medicines Agency, 2002 Company Report, 18, 2002.

122. Walker, A. M., "The Relation Between Voluntary Notification and Material Risk in Dietary Supplement Safety," Report prepared for the Food and Drug Administration, 2000.

123. Food and Drug Administration, Letter from Melinda Plaisier to Congressman Henry Waxman (CA) dated July 11, 2001 and Tab C (preliminary evaluation of data from American Association of Poison Control Centers) enclosed with the letter, 2001.

124. U.S. General Accounting Office (GAO), GAO Report, "Dietary Supplements: Uncertainties in Analyses Underlying FDA's Proposed Rule on Ephedrine Alkaloids," GAO, 1999, submitted to Docket No. 2000N-1200, BKG 1, vol. 32.

125. Boozer, C. N., J. A. Nasser, S. B. Heymsfield, et al., "An Herbal Supplement Containing Ma Huang-Guarana For Weight Loss: A Randomized, Double-Blind Trial," *International Journal of Obesity and Related Metabolic Disorders*, vol. 25, pp. 316-324, 2001.

126. National Institutes of Health, National Heart, Lung, and Blood Institute, Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report, NIH Publication No. 02-5215, 2002 (<http://www.nhlbi.nih.gov/guidelines/cholesterol>) set

127. Bray, G. A. and F. L. Greenway, "Current and potential drugs for treatment of obesity," *Endocrine Reviews*, vol. 20, pp. 805-875, 1999.

128. Yanovski, S. Z. and J. A. Yanovski, "Obesity," *New England Journal of Medicine*, vol. 346, pp. 591-602, 2002.

129. Food and Drug Administration, Division of Metabolic and Endocrine Drug Products, FDA Draft Guidance for the Clinical Evaluation of Weight-Control Drugs, 1996.

130. International Committee on Harmonization (ICH): Guidance for Industry. *S7A Safety Pharmacology Studies for Human Pharmaceuticals*, ICH, pp. 1-11 (<http://www.fda.gov/cder/guidance/4461fnl.pdf>), 2001.

131. Filozof, C., C. Gonzalez, and E. Hofman, "The Effect Ephedrine Plus Caffeine After a 4-week Portion-Controlled Diet," *Ninth International Congress on Obesity*, Abstract 591, *Ninth International Congress on Obesity*, vol. 26, suppl. 1, p. S156, 2002, August 2002.

132. Food and Drug Administration, "Evidence On The Safety And Effectiveness Of Ephedra: Implications For Regulation," (<http://www.fda.gov/bbs/topics/NEWS/ephedra/whitepaper.html>), 2003.

133. Boerth, J. M., C. F. Caley, "Possible Case of Mania Associated With Ma-huang," *Pharmacotherapy*, vol. 23, pp. 380–383, 2003.

134. Samenuk, D., M. S. Link, M. K. Homoud, et al., "Adverse Cardiovascular Events Temporally Associated With Ma-huang, an Herbal Source of Ephedrine," *Mayo Clinic Proceedings*, vol. 77, pp. 12–16, 2002.

135. Bent, S., T. N. Tiedt, M. C. Odden, et al., "The Relative Safety of Ephedra Compared With Other Herbal Products," *Annals of Internal Medicine*, vol. 138, pp. 468–471, 2003.

136. Morgenstern, L. B., C. M. Viscoli, W. N. Kernan, et al., "Use of Ephedra-Containing Products and Risk for Hemorrhagic Stroke," *Neurology*, vol. 60, pp. 132–135, 2003.

137. Food and Drug Administration, Nightingale, S. L., FDA "Dear Colleague" Letter Regarding the Research on Eosinophilia-Myalgia Syndrome and Current Regulatory Status of L-Tryptophan, 1992 (<http://www.cfsan.fda.gov/~dms/ds-ltr3.html>).

138. Food and Drug Administration, Policy and Guidance Handbook For FDA Advisory Committees, pp. 113–114, 1994.

139. Chyka, P. A., McCommon, S. W., "Reporting of adverse drug reactions by poison control centres in the U.S.," *Drug Safety*, vol. 23, pp. 87–93, 2000.

140. Office of Management and Budget: Regulatory Analysis, Circular A–4 (<http://www.whitehouse.gov/omb/circulars/a004/a-4.html>), 2003.

per last changes

134. Samenuk, D., Link, M. S., Homoud, M. K., Contreras, R., Theohardes, T. C., Wang, P. J., Estes, N. A., III, "Adverse cardiovascular events temporally associated with ma huang, an herbal source of ephedrine," *Mayo Clinic Proceedings* 77:12–16, 2002.

135. Bent, S., Tiedt, T. N., Odden, M. C., Shlipak, M. G., "The relative safety of ephedra compared with other herbal products," *Annals of Internal Medicine* 138:468–471, 2003.

136. Morgenstern, L. B., Viscoli, C. M., Kernan, W. N., Brass, L. M., Broderick, J. P., Feldmann, E., Wilterdink, J. L., Brott, T., Horwitz, R. I., "Use of Ephedra-containing products and risk for hemorrhagic stroke," *Neurology* 60:132–135, 2003.

~~137~~ 137. Food and Drug Administration, Nightingale, S. L., FDA "Dear Colleague" letter regarding the Research on Eosinophilia-Myalgia Syndrome and Current Regulatory Status of L-Tryptophan, 2002. <http://www.cfsan.fda.gov/~dms/ds-ltr3.html>.

~~138~~ 138. Food and Drug Administration, Policy and Guidance Handbook For FDA Advisory Committees, p. 114 (1994)

139. Chyka, P. A., McCommon, S. W., "Reporting of adverse drug reactions by poison control centres in the US," *Drug Safety* 23:87–93, 2000.

140. Office of Management and Budget: Regulatory Analysis, Circular A–4:2003. <http://www.whitehouse.gov/omb/circulars/a004/a-4.html>.

141. Shekelle P, Morton, S., Maglione M, et al., "Ephedra and Ephedrine for Weight Loss and Athletic Performance Enhancement: Clinical Efficacy and Side Effects. Evidence Report/Technology Assessment," No. 76 (Prepared by Southern California Evidence-based Practice Center, RAND, under Contract No 290–97–0001, Task Order No. 9). AHRQ Publication No. 03–E022. Rockville, MD: Agency for Healthcare Research and Quality, Table 23, 2003.

142. Centers for Disease Control and Prevention, "Life Expectancy" (Data are for U.S. in 2001). National Center for Health Statistics, Centers for Disease Control and

141. Shekelle P, S. Morton, M. Maglione, et al., "Ephedra and Ephedrine for Weight Loss and Athletic Performance Enhancement: Clinical Efficacy and Side Effects. Evidence Report/Technology Assessment," No. 76 (Prepared by Southern California Evidence-Based Practice Center, RAND, under Contract No. 290-97-0001, Task Order No. 9), AHRQ Publication No. 03-E022, Rockville, MD, Agency for Healthcare Research and Quality, Table 23, 2003.

142. Centers for Disease Control and Prevention, "Life Expectancy" (Data are for U.S. in 2001). National Center for Health Statistics, Centers for Disease Control and Prevention, U. S. Department of Health and Human Services (<http://www.cdc.gov/nchs/fastats/lifexpec.htm>), accessed on December 9, 2003.

143. Derdeyn, C. P., Powers, and W. J., "Cost-Effectiveness of Screening for Asymptomatic Carotid Atherosclerotic Disease," *Stroke*, vol. 27, pp. 1944-1950, 1996.

144. Agency for Healthcare Research and Quality (AHRQ), Healthcare Cost and Utilization Project, 2001 National Statistics, The "National Bill" for Conditions Treated in Hospitals (Top 100 Clinical Classifications Software (CCS) Diagnoses), (<http://www.hcup.ahrq.gov/HCUPnet.asp>), 2001 .

145. GNC Plans to Drop Ephedra Private-Label Supplements, *FDC Reports—Tan Sheet*, pp. 11-12, 1996.

146. Redfearn, S., "Ephedra Products Thin Out: Braced for the Worst, Makers Sell New Herbs," *The Washington Post*, HE01, 2003 (<http://www.washingtonpost.com/wp-dyn/articles/A52270-2003Jan13.html>).

147. Letter Correction: The Relative Safety of Ephedra Compared with Other Herbal Products, *Annals of Internal Medicine*, vol. 138, pp. 1012, 2003 (<http://www.annals.org/cgi/content/full/138/12/1012>), accessed on June 17, 2003. ^{December 11, 2003}

148. Dickinson, A., Letter, "The Relative Safety of Ephedra Compared With Other Herbal Products," *Annals of Internal Medicine*, ^{vol. 139, pp.} 139/385-386 (http://www.annals.org/cgi/content/full/139/5__Part__1/385-b) 2003, accessed on September 2, 2003.

per
Connie's



149. Nutrition Business Journal, 2002 Facts and Stats about Dietary Supplements

(obtained from <http://www.nnfa.org/facts>), 2002.

150. Kaufman, D. W., Kelly, J. P., Mitchell, A. A., "Use of Ephedra-Containing Products in the U.S. Population," *Data from the Slone Survey*, FDA Docket No. 1995N-0304, emc126, vol. 297, 2003.

151. Research Triangle Institute, "Cost of Reformulating Foods and Cosmetics," Final Report, Report Prepared for the Food and Drug Administration, RTI Project Number 08184.003, 2002.

152. Gugliotta, G., "Ephedra Lawsuits Show Big Increase," *The Washington Post* ^{5/1 July 23, 2000} (<http://www.washingtonpost.com/ac2/wp-dyn?pagename=article&node=&contentId=A25415-2000Jul21¬Found=true>), ~~July 23, 2000~~, accessed on February 3, 2004.

153. Gugliotta, G., "Woman Wins \$13.3 Million Against Dietary Company," *The Washington Post* (<http://www.washingtonpost.com/ac2/wp-dyn?pagename=article&node=&contentId=A40923-2001Feb7¬Found=true>, February 2, 2001), accessed on February ~~2~~³, 2004. ✓

154. Prevention Magazine, "Consumer Use of Dietary Supplements," 1999.

155. National Consumers League, National Consumers League's Survey of Consumers Using Over-the-Counter (OTC) Medications, 2003.

156. Geiger, C. J., "Health Claims: History, Current Regulatory Status, and Consumer Research," *Journal of the American Dietetic Association*, vol. 98, pp. 1312-1322, 1998.

157. MacKinnon, D. P., L. Nohre, J. Cheong, et al., "Longitudinal Relationship Between the Alcohol Warning Label and Alcohol Consumption," *Journal of Studies on Alcohol*, vol. 62, pp. 221-227, 2001.

158. Food and Drug Administration, Memorandum: Label Analysis for Dietary Supplements Containing Ephedrine Alkaloids, January 28, 2004.

152. Gugliotta, G.: Lawsuits over *Ephedra* on the Rise. The Washington Post 6-23-2000. http://www.judgmentofparis.com/Liis_News.htm#Ephedra6/23/2000

153. Gugliotta, G.: Woman Wins \$13.3 Million Against Dietary Company. The Washington Post 2-8-2001. <http://www.crnusa.orgmshellmedia020901wpcopy.html2/8/2001>

154. Prevention Magazine: Consumer Use of Dietary Supplements. 1999. 1999

155. National Consumers League: National Consumers League's Survey of Consumers Using OTC. 2003. 2003

156. Geiger, C. J.: Health claims: history, current regulatory status, and consumer research. *J Am Diet Assoc* 98:1312-1322, 1998. PM:9813589

157. MacKinnon, D. P., Nohre, L., Cheong, J., Stacy, A. W., Pentz, M. A.: Longitudinal relationship between the alcohol warning label and alcohol consumption. *J Stud Alcohol* 62:221-227, 2001. PM:11327188

158. Research Triangle Institute: Dietary Supplement Sales Information. Final Report. Contract No. 223-96-2290 Task Order 4:1999. <http://www.foodriskclearinghouse.umd.edu/dspd.htm10/1999>

159. Research Triangle Institute: Survey of Manufacturing Practices in the Dietary Supplement Industry. *Final Report*. RTI Project Number 6673-6:5-17-2000. <http://www.foodriskclearinghouse.umd.edu/smpds.htm5/17/2000>

List of Subjects in 21 CFR Part 119

Dietary ingredients, dietary supplements, foods.

JDH p. 2-18
2-19

■ Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 119 is added as follows:

■ 1. Part 119 consisting of § 119.1 is added to read as follows:

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159. Research Triangle Institute, Dietary Supplement Sales Information, Supplement to the Final Report, Report Prepared for the Food and Drug Administration, Contract No. 223-96-2290 Task Order 4:1999 (<http://www.foodriskclearinghouse.umd.edu/dspd.htm>), accessed ^{8th} October 1999.

160. Research Triangle Institute, Survey of Manufacturing Practices in the Dietary Supplement Industry. Final Report, Report prepared for the Food and Drug Administration, RTI Project Number 6673-6:2000 (<http://www.foodriskclearinghouse.umd.edu/smpds.htm>), accessed on May 17, 2000.

161. Office of Management and Budget, *Guidance for Implementing E.O. 13132, "Federalism,"* October 28, 1999.

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PART 119—DIETARY SUPPLEMENTS THAT PRESENT A SIGNIFICANT OR UNREASONABLE RISK

§ 119.1 Dietary supplements containing ephedrine alkaloids.

Dietary supplements containing ephedrine alkaloids present an unreasonable risk of illness or injury under conditions of use recommended or suggested in the labeling, or if no conditions of use are recommended or suggested in the labeling, under ordinary conditions of use. Therefore, dietary supplements containing ephedrine alkaloids are adulterated under section 402(f)(1)(A) of the Federal Food, Drug, and Cosmetic Act.

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Authority: 21 U.S.C. 321, 342, 343, 371. ✓

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Since only 1 section is being added, place the authority at the end OFC/gd

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