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January 29, 2004

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FROM
JAKILYN
1-29-04

Food and Drug Administration

21 CFR Part 111

[Docket No. 1995N-0304]

RIN 0091-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) is issuing a final regulation declaring dietary supplements containing ephedrine alkaloids adulterated 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 the 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.

we are currently unaware of any such use, and our experience with ephedrine alkaloid-containing OTC drug products suggests that such benefits will be demonstrable only for disease uses.

B. What Are the Ephedrine Alkaloids and Where Do They Come From?

The ephedrine alkaloids, including, among others, ephedrine, pseudoephedrine, norephedrine, methylephedrine, norpseudoephedrine, methylpseudoephedrine, are chemical stimulants that occur naturally in some botanicals (Refs. 1 through 5), but can be synthetically derived. The ingredient sources of the ephedrine alkaloids in dietary supplements include raw botanicals (i.e., plants) and extracts from botanicals. Ma huang, *Ephedra*, Chinese *Ephedra*, and epitonin 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 (Refs. ~~9~~^{9 and} 10).

with these adverse events; review of the use of *Ephedra* species in traditional Asian medicine; analysis of the likelihood and factors affecting the reporting of adverse events; and summaries of the known physiological, pharmacological, and toxic effects of ephedrine alkaloids (Ref. 18). This announcement was made in part to prepare for a meeting convened by the Department of Health and Human Services (DHHS) Office of Women's Health (OWH) in August 2000 to discuss information about the safety of dietary supplements containing ephedrine alkaloids. Shortly before that meeting, FDA announced (65 FR 46721, July 31, 2000) that it would again reopen the comment period for the 1997 proposed rule from August 10, 2000 (the day after the OWH meeting) until September 30, 2000. In that notice, we also announced the availability of a report on phenylpropanolamine and hemorrhagic stroke (Ref. 19).

In April 2001, DHHS's Office of Inspector General issued a report entitled "Adverse Event Reporting For Dietary Supplements: An Inadequate Safety Valve" (Ref. 20) that assessed the effectiveness of the FDA's Adverse Event Reporting System. This report found that adverse event reporting systems typically detect only a small proportion of the events that actually occur.

On March 5, 2003, we published a notice in the **Federal Register** making available new information about dietary supplements containing ephedrine alkaloids and requesting public comment on the new information and on regulation of these products (68 FR 10417, March 5, 2003). We specifically sought comments on whether, in light of current information, we should determine that dietary supplements containing ephedrine alkaloids are adulterated because they present a significant or unreasonable risk of illness or injury under the conditions of use recommended or suggested in labeling

or under ordinary conditions of use if the labeling is silent. The notice also sought comment on a revised version of the warning statement first proposed on June 4, 1997. The revised warning statement had two components, a short warning that would be required to appear on the principal display panel (PDP) and a longer warning that could appear elsewhere in labeling. The proposed PDP warning stated that strokes, heart attacks, seizures, and death have been reported after consumption of dietary supplements containing ephedrine alkaloids and that the risks of adverse events increase with strenuous exercise and with use of other stimulants, including caffeine. The longer proposed warning included more detailed information about risks associated with the use of the product and recommended that consumers avoid using the product and/or consult a doctor under certain circumstances.

In the March 2003 notice, we asked for public comment on all additional evidence developed since the publication of the June 1997 proposal. One such study was a report by the Southern California Evidenced Based Practice Center (the RAND report, ^{or RAND ~~report~~} ^{or RAND Cooperative}), commissioned by the National Institutes of Health (NIH) (Refs. 21 and 22). RAND reviewed recent evidence on the risks and benefits of ephedra and ephedrine² and found that dietary supplements

² The RAND report uses the term “ephedra” to refer to ephedrine alkaloids from botanical sources, whether or not they are contained in dietary supplements. RAND uses the term “ephedrine” to refer to pharmaceutical sources of ephedrine.

³ RAND defined a “sentinel event” as a case that met all three of the following criteria: (1) Documentation of an adverse event that met the selection criteria; (2) documentation that the person having the adverse event took an ephedra-containing supplement or ephedrine within 24 hours prior to the event (for cases of death, myocardial infarction [heart attack], stroke, or seizure); and, (3) documentation that alternative explanations for the adverse event were investigated and were excluded with reasonable certainty. These criteria were subject to procedures which included the following (among other procedures): medical record documentation that an adverse event had occurred; documentation that the subject had consumed ephedra or ephedrine within 24 hours prior to the adverse event, or that a toxicological examination revealed ephedrine or one of its associated products in the blood or urine. Cases with no such documentation were not reviewed further. For the Metabolife cases, ephedra was assumed to have been used within the prior 24 hours for all but psychiatric events. All cases of stroke that met the criterion of having consumed ephedra or ephedrine within 24 hours were reviewed in more detail; to be classified as a “sentinel event,” reports of thrombotic stroke needed to have an assessment for a hypercoagulable state

- An FDA preliminary analysis of data collected by and purchased from the American Association of Poison Control Centers (AAPCC) that showed an increase in the number of ephedrine alkaloid-related AERS from 211 in 1997 to 407 in 1999; and
- Adverse events reported to Public Citizen.

The petition also cited the known pharmacological and toxicological properties of ephedrine alkaloids, recent published articles and case reports, the fact that adverse events are invariably underreported, and the lack of any evidence of long-term benefits for the products.

We have considered the information submitted by these petitions, as well as the comments received in response to these petitions and all other information in the docket. For the reasons summarized in section I.A of this document, we have concluded that dietary supplements containing ephedrine alkaloids are adulterated. ✓

II. Summary of Letters and Comments

We have received more than 48,000 comments in three dockets pertaining to ephedrine alkaloids, Docket Nos. 95N-030~~3~~4, 00N-1200, and 01P-0396. —

These comments include all letters received prior to the June 1997 proposal, all comments received in response to **Federal Register** notices, and all submissions related to public meetings pertaining to dietary supplements containing ephedrine alkaloids. The 48,000 comments include more than 41,000 form letters received in the 1997 docket. Many comments submitted identical or nearly identical statements to more than one docket or in response to more than one **Federal Register** notice. Most of the comments were submitted by individual consumers who use dietary supplements containing ephedrine alkaloids or by independent distributors of these products. Other

compounds are pharmacologically active substances in the plant. Therefore, we considered all of them in our evaluation of the risks associated with the use of the botanical or extracts from the botanical. However, as discussed in the response to comment 24 in section ~~VIA~~^{V.B.1} of this document, we recognize that there are some differences between ephedrine and PPA.

(Comment 2) Several comments asked whether North American species of *Ephedra* (e.g., Mormon Tea) are covered in this rulemaking.

(Response) Most North American species of *Ephedra* (e.g., Mormon tea) do not contain ephedrine alkaloids (Refs. 2 and 26). Nonetheless, any dietary supplement that contains ephedrine alkaloids from any botanical source, including from a North American species of *Ephedra*, is subject to this rulemaking. ✓

IV. Legal Issues

A. What Is Our Legal Authority Under the Act?

We are issuing this final regulation under sections 402(f)(1)(A) and 701(a) of the act (21 U.S.C. 371(a)). Section 402(f)(1)(A) of the act deems a food to be adulterated:

If it is a dietary supplement or contains a dietary ingredient that—

(A) presents a significant or unreasonable 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.

This regulation makes a finding that dietary supplements containing ephedrine alkaloids are adulterated because they present an unreasonable risk within the meaning of section 402(f)(1)(A) of the act. This finding is based on our conclusion that the risks of these products outweigh their benefits. Our

legal interpretation of “unreasonable risk” is discussed in detail in section V.D.1 of this document. This regulation does not address the meaning of “significant risk” or whether dietary supplements containing ephedrine alkaloids present a significant risk under section 402(f)(1)(A).

Section 701(a) of the act gives FDA authority to issue regulations for the efficient enforcement of the act. We are using this rulemaking authority for dietary supplements containing ephedrine alkaloids because we are articulating a standard for unreasonable risk under 402(f)(1)(A) of the act for the first time and because it is more efficient to declare these products adulterated as a category than to remove them from the market in individual enforcement actions in which we would have to establish, for each individual product, that they present a significant or unreasonable risk.

The March notice asked about the adequacy of FDA’s authority to regulate dietary supplements containing ephedrine alkaloids. More specifically, we sought comments on “what additional legislative authorities, if any, would be necessary or appropriate to enable us to address this issue most effectively” (68 FR 10417 at 10420).

(Comment 3) Many comments expressed the view that we already have the authority we need to take action against dietary supplements containing ephedrine alkaloids. These comments cited our authority to declare these supplement products to be a significant or unreasonable risk or imminent hazard under section 402(f)(1) of the act or to regulate the products as containing a poisonous or deleterious substance that may render them injurious to health under section 402(a). The comments differed as to whether we had the necessary evidence to utilize these provisions. Several comments

Congressional action rather than rulemaking. Therefore, we are not addressing those suggestions in this rule.

(Comment 5) One comment stated that conventional food safety standards, i.e., the generally recognized as safe (GRAS) standard or the standard for FDA approval as a food additive, do not apply to dietary ingredients.

(Response) We agree that the standards referred to in this comment do not apply to dietary ingredients. Premarket approval is required of substances that are food additives as defined in section 201(s) of the act. Substances that would otherwise fall under the food additive definition but are generally recognized as safe by experts are not food additives and do not require premarket approval. Dietary ingredients contained in, or intended for use in, a dietary supplement are explicitly excluded from the food additive definition in section 201(s)(6) of the act. Therefore, neither the premarket approval regime for food additives nor the ~~generally recognized as safe (GRAS)~~ standard applies to dietary ingredients. We are instead basing this final rule on the dietary supplement adulteration standard set forth in section 402(f)(1)(A) of the act.

(Comment 6) One comment stated we are violating the First Amendment of the U.S. Constitution and the Administrative Procedure Act (APA) by requiring a much higher standard of safety for dietary supplements than for conventional foods. Another comment also raised concerns about the First Amendment limits of FDA's authority to regulate dietary supplements containing ephedrine alkaloids.

(Response) We disagree with these comments. There are a number of different safety standards for foods (see, e.g., section 402(a)(1) and section 402(a)(2)(C) of the act), and whether these standards are higher or lower than the "significant or unreasonable risk" standard for dietary supplements in

likely benefits, not speculative benefits. A reasonably likely benefit is one that is supported by a meaningful totality of the evidence, given the current state of scientific knowledge, though the evidence need not necessarily meet the approval standard for a prescription drug.

Although Congress placed the burden on FDA to show “unreasonable risk,” once a danger is identified, we do not believe that Congress intended us to delay action until double-blind, placebo-controlled clinical studies could be conducted or that no action be taken if such clinical studies are infeasible or unethical (see the response to comment ¹⁹21). While such studies are the “gold standard” for determining effectiveness, they are not always available for dietary supplements because DSHEA does not require companies to conduct such studies before marketing a dietary supplement. DSHEA also does not require post-marketing safety and adverse event reporting from dietary supplement manufacturers. Accordingly, FDA is relying on the available scientific data and literature to support its conclusion that dietary supplements containing ephedrine alkaloids present an “unreasonable risk.” The government’s burden of proof for “unreasonable risk” can be met with any science-based evidence of risk and does not require a showing that the substance has actually caused harm in particular cases.

For example, there is clear scientific evidence that a sustained increase in blood pressure increases the risks of cardiovascular disease (Ref. ~~29~~^{29a}30). Thus, a dietary supplement that caused a sustained rise in blood pressure across the population would increase the risk of cardiovascular events including stroke, heart attack, or death to that population. Even risks that may not be detectable in small studies or studies of short duration (which are not designed to detect such risks at a statistically significant level) could, over

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 transiently.

Sympathomimetic effects raise three concerns. First, sympathomimetics can induce cardiac arrhythmias in susceptible people, such as those with underlying coronary artery disease. Second, increased mortality has been observed in patients with congestive heart failure who were treated with sympathomimetic drugs, such as beta-agonists (early studies using such drugs as albuterol led to adverse outcomes) and xamoterol (Ref. 38), as well as phosphodiesterase inhibitors, which potentiate (increase the effect of) the effects of beta-agonists, including milrinone (Ref. 39) and enoximone (Ref. 40). The studies that showed these adverse effects occurred in about 3 months of product use. Third, sympathomimetics can raise blood pressure (Ref. 41).

Based on clinical data, the ephedrine alkaloids present in dietary supplements would be expected to have the same or similar effects as other sympathomimetics on heart rate and blood pressure. Controlled clinical trials using products containing ephedrine alkaloids confirm their typical sympathomimetic effects. Single-dose studies of dietary supplements containing ephedrine alkaloids show that these products cause increases in both heart rate and blood pressure in healthy subjects (Ref. 42–44). In one such study of a dietary supplement containing ephedrine alkaloids, the peak increase in blood pressure following a single oral dose of ephedrine alkaloids and caffeine (20 mg/200 mg) was 14 mm Hg systolic and 6 mm Hg diastolic, occurring about 2 hours after the single dose was taken. ~~Haller, 2002 214 /id.~~ 

The findings from these studies are complicated by the presence of caffeine in the dietary supplements used because caffeine is also known to

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 blood pressure monitoring device (ABPM); the ABPM method provides more frequent measurements of blood pressure and is, therefore, better able to evaluate blood pressure effects over time. The ephedrine alkaloids and caffeine-treated subjects did not show a difference in the blood pressure measurements taken at the clinic, but did show statistically significant higher average blood pressure measurements over 24 hours at week 4 measured by ABPM (approximately 4 mm Hg for both systolic and diastolic blood pressure) when compared to placebo treated subjects. The ABPM results are shown in a table in the paper. The difference in blood pressure between the two groups represented the sum of small downward changes in the placebo group (compared to baseline) and small upward changes, or no change, in the ephedra group. Boozer et al. reported numerous breakdowns of these data (e.g., 6 am to midnight and midnight to 6 am) and characterized the difference between the ephedra and placebo groups as small (about 3 mm Hg) but for the most common ABPM measure, 24 hour value, the difference was 4/4 mm Hg. The observation that this difference (shown in Table 2 of the paper) (Ref. 49). reflected a fall in blood pressure in the placebo group as much as a rise in blood pressure in the ephedra group is not relevant. The only controlled and, therefore, reliable observation is the comparison of the two groups. Small changes from baseline can occur for a wide variety of reasons and are commonly observed in placebo and treated groups. Therefore, the ABPM data are important because they demonstrate that the effect of the ephedrine alkaloids, including dietary supplements containing ephedrine alkaloids, on blood pressure is not transient, but is still evident after one month of continued

*Check Appendix
safety (2)*

exposure (when measured by ABPM) and, therefore, would be expected to persist long term. The effect reported in the Boozer, et al. (2002) study cannot be attributed to the caffeine because the effect of caffeine on blood pressure (discussed above) is transient, and the acute effect of caffeine to increase blood pressure is lost within two weeks of continued use (Ref. ^{45, 46} 46, 50). 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. 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.

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 51), Richard L. Atkinson, M.D. (Ref. ⁵¹ 52), and Mark Espeland, Ph.D. (Ref. ⁵² 53). 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 the 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., 1–2 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 (Ref. 29, 54).

The extremely high prevalence of diagnosed and undiagnosed hypertension in the United States 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. 49) one of great concern. Reductions in blood pressure of this magnitude (i.e., around 4 mmHg 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 (Ref. 55, 56, 57). 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).

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 mmHg systolic and less than 90 mmHg diastolic) (Ref. 29, 30). This indicates that many people would be at an increased risk with long-term use of dietary supplements containing ephedrine alkaloids. Studies of hypertension

treatments suggest that this increase in risk would occur fairly quickly in hypertensive individuals. Anti-hypertensive drugs that lower blood pressure by 4–6 mm Hg have been shown to significantly decrease the occurrence of cardiovascular morbidity (stroke, heart attack) and mortality (Ref. ^{55, 57, 59} ~~56, 58, 59~~).  This effect is evident within 6–12 months in large outcome studies (Ref. 29,30). ✓

FDA is concerned about the adverse health effects that can occur with the use of agents that raise blood pressure, such as dietary supplements containing ephedrine alkaloids, for short- or long-term use. Even in the case of a controlled clinical trial of a possible hypertension treatment where subjects are closely monitored, we advise sponsors to limit the length of time subjects can be in a placebo/untreated group to about 8 weeks to minimize their exposure to cardiovascular risks from the absence of treatment.

As noted above, the pharmacological effects of ephedrine alkaloids also present increased short-term risks of adverse health events in susceptible populations. For example, there is evidence from peer-reviewed scientific literature that a wide range of drugs with sympathomimetic activity, including beta-agonists, phosphodiesterase inhibitors, and dobutamine, have adverse effects (increased mortality due to heart failure and sudden death) in patients studied with congestive heart failure. These effects have been seen in relatively short-term studies (Ref. ^{59, 60} ~~60, 61~~) (Ref. ⁶¹ ~~62~~)  Similarly, there are studies that document that people with coronary artery disease are more susceptible to the well-known pro-arrhythmic effects of sympathomimetics (Ref. ^{62, 63} ~~63, 64~~) (Ref. ⁶⁴ ~~65~~) 

The occurrence of such an arrhythmic event is not one that requires prolonged exposure but would represent a risk associated with each use, including the first. Many individuals are unaware that they have coronary artery disease or early heart failure because these conditions may not cause prominent

symptoms until later in the course of these conditions. As a result, we are concerned that such individuals will not know that they are at an increased risk for developing significant cardiovascular adverse events from even short-term use of dietary supplements containing ephedrine alkaloids. Overweight and obese individuals are particularly prone to hypertension, coronary artery disease, and/or heart failure, as overweight and obesity are associated with these conditions (Ref. 66,67). ^{US Law} These conditions may not manifest clinically until later in the course of the condition and, therefore, individuals, including overweight and obese individuals, may be unaware they have these conditions. As a population, the overweight and obese are, thus, at a greater risk even from short-term use of sympathomimetics.

As summarized above, the comments cited certain literature suggesting the possibility of additional adverse effects of ephedrine alkaloids, such as prolonged bleeding in those who undergo surgery. Given the clear scientific evidence of this cardiovascular risks presented by dietary supplements containing ephedrine alkaloids, we have not relied on these other possible adverse effects noted in the comments in our determination of unreasonable risk.

(Comment 23) Various comments did not agree that there are risks with products containing ephedrine alkaloids and stated the opinion that cardiovascular side effects associated with products containing ephedrine alkaloids in several blinded studies were not significantly different in control and treatment groups. Several comments maintained that there is no evidence from clinical studies that ephedrine “supplementation” increases peak heart rate, peak blood pressure, or the prevalence of cardiac arrhythmias. Another comment contended that “clinically relevant doses” of ephedra have no

clinically significant effect on pulse or blood pressure, and produce no measurable alterations in myocardial function. A number of comments noted that changes in heart rate and blood pressure are transient and similar to those produced by exercise. Several comments stated that the effects of ephedra combined with caffeine on blood pressure are modest and generally subside over the first few days of use. Other comments stated that, although dietary supplements containing ephedrine alkaloids have a relatively high incidence of subjective and cardiovascular side effects with first use, the side effects diminish with continued use due to tachyphylaxis. Several comments noted that the literature, including the obesity studies we cited in the proposed rule (Ref. ~~36,68-81~~^{36,67-80}), indicated that tachyphylaxis sets in within a few days, at the most a few weeks, and results in a dramatic decrease in the likelihood of adverse events. Another comment suggested that pharmacological studies showed that peak ephedrine levels are reached within 1 to 4 days and that no further accumulation occurs thereafter. Another comment suggested that this fact means ephedrine alkaloids pose no risk of long-term toxicity.

One comment noted that ephedrine alkaloids are not toxic in the classic sense, that is, do not cause organ changes or damage to the metabolism. Other comments suggested that the available pathology data do not show any pattern consistent with ephedrine alkaloids as a cause of death.

(Response) We do not agree that ephedrine alkaloids pose no risk of adverse consequences. The suggestion that the cardiovascular effects of ephedrine alkaloids persist for only a few days is not supported by the Boozer et al. (2002) study (Ref. 49), which demonstrated a higher blood pressure (compared with placebo) at the end of one month of therapy. This difference was observed when blood pressure was measured throughout the day, using

ABPM, but not with cuff blood pressure measurements (a less sensitive measure). This difference in results using different measurement methods may have confused some readers and led them to conclude that ephedrine alkaloids do not have a clinically meaningful effect on blood pressure. The fact that an effect on blood pressure (as measured using ABPM, which follows measurements throughout the day) was still present at one month strongly indicates that tachyphylaxis to the effects of ephedrine does not occur. As discussed in the response to comment 22, tachyphylaxis tends to occur rapidly, as with caffeine, whose blood pressure raising effect is lost within two weeks. Therefore, FDA does not agree with the comments expressing assurances that adverse effects will disappear with continued use of ephedrine alkaloids because of tachyphylaxis.

Additionally, some of the studies cited by the comments apparently measured cuff blood pressure only around the time of dosing, when minimal serum concentrations of ephedrine alkaloids and effects on blood pressure would be expected. Absence of an effect at this time cannot be seen as evidence that ephedrine alkaloids do not increase blood pressure.

The suggestion that “clinically relevant” or “clinically significant” doses of ephedrine have no effects on blood pressure is unsupported by the available data. What constitutes a “clinically relevant or significant” dose is undefined (and unlikely to be definable given the nature of the available efficacy data for ephedrine alkaloids). The difficulties in using the available clinical data to obtain such reassurance with regard to the safe use of ephedrine are discussed in *the response to comment 26* ~~section xx~~ of this document.

We do not agree that the clinical studies establish that ephedrine does not have adverse pharmacological and clinical effects. The published controlled

studies of the use of ephedrine alkaloid products for weight loss cited by these comments cannot establish the safety profile of these products. First, many of the most serious risks, such as strokes or heart attacks (consequences of elevated blood pressure), arrhythmias, or worsened heart failure, are relatively infrequent or are delayed and, therefore, will not be detected in studies using small populations (such as under 100 patients per group) as these studies did. Second, these studies often had other important design limitations, such as lack of adequate controls (including the absence of placebo groups in some studies), and inadequate information about the causes that led to participants dropping out of the trial. In addition, persons with known cardiovascular disease or cardiovascular risks were usually excluded. Thus, these studies were not designed to detect serious adverse effects in susceptible individuals, nor to detect adverse effects that occur infrequently. As discussed below, these studies were also not adequately designed to assess blood pressure effects. Given these limitations, it is not surprising that these published studies do not report serious adverse events. (Ref. 21,22) (Ref. 50,51,71, 51,53,82).  Last citation is for summary table for administrative record, where the studies are individually evaluated here]

These trials also would not have been able to detect effects on blood pressure because of other design limitations. For example, when sponsors of drug products seek to detect a drug-induced decrease in blood pressure in patients with hypertension, the trial is specifically designed: 1) to assess the blood pressure effects at both peak and trough levels of the drug in the blood, and 2) to measure blood pressure in a consistent and reproducible manner. This typically requires the enrollment of at least 100 patients to detect a difference from placebo of around 4 - 6 mm Hg systolic, multiple measures

at each time point and careful attention to how blood pressure is measured. These design features are either lacking or not described in the publications cited by the comments summarized above, significantly limiting the trials' ability to detect any differences between the treatment and placebo groups with regard to blood pressure or heart rate. With regard to the timing of the measurement, the blood pressure measures appear to have been made at (or shortly after) the administration of the product containing ephedrine for almost all of the published trials. Absorption of the new dose would be minimal or incomplete and the dose taken the day before (8–12 hours earlier) would have been substantially removed from the circulation, given ephedrine's approximately 4-hour half-life. Blood levels of ephedrine would thus be at or near their lowest values of the day ("trough level"), a time when minimal effects on blood pressure would be anticipated. Measurements made only at trough level might well miss a significant effect on blood pressure that would have been seen at or near peak concentrations of ephedrine. Thus, although some published studies on the cardiovascular effects of ephedrine (especially blood pressure) over a period of weeks or months have reported little or no effect of ephedrine on blood pressure and a variable effect on heart rate, these studies are severely limited in their ability to establish safety, such that the true effects of ephedrine on heart rate and blood pressure cannot have been adequately assessed.

We do not agree with the comments that state that ephedrine alkaloids are not toxic because they do not induce specific organ pathology. Persistently elevated blood pressure can result in defined cardiovascular toxicity (Ref. 29, 29, 51, 8, 29, 55), as can ephedrine's sympathomimetic effects in people with coronary artery disease or heart failure, but the kinds of damage seen in humans from

selection bias, and confounding. One comment complained that we reopened the ephedra docket requesting comment on the HSP, but we did not place in the docket, or request comment on, the many published and unpublished clinical studies submitted by one trade organization to support PPA's safety. The comment asserted that our review of the pharmacology of ephedrine alkaloids did not include most of the pivotal information on PPA submitted to us by the Consumer Healthcare Products Association (CHPA). Another comment expressed the view that, in our review of safety data related to ephedra, we should avoid relying on safety data concerning other ingredients.

(Response) ^{The substance,} l-norephedrine, also known as (-)-norephedrine, refers to the isomeric portion of PPA that occurs naturally in *Ephedra* and as a metabolite of ephedrine in the body. We agree that the l-norephedrine in racemic PPA is a metabolite of ephedrine, and further that ephedrine and its metabolites have potent vasoactive properties, reinforcing the view that dietary supplements containing ephedrine alkaloids have the pharmacological properties described in the response to comment 22. These properties, in turn, are linked to predictable adverse clinical outcomes both in the general population (e.g., increased blood pressure) and in susceptible populations (e.g., cardiac arrhythmias). Although there are some similarities between PPA and ephedrine, there are also differences. PPA shows tachyphylaxis to rises in blood pressure within approximately 24 hours and usage has been linked to hemorrhagic strokes (bleeding strokes due to a ruptured blood vessel). Ephedrine does not show such tachyphylaxis. In addition, use of ephedrine has been associated with ischemic strokes (a blood clot blocking off an artery causing a lack of oxygen to portions of the brain), but not hemorrhagic strokes.

The major alkaloid in most dietary supplements containing ephedrine alkaloids is generally ephedrine, and not norephedrine. ^(Ref. 82)

Therefore, we have not relied on the HSP or spontaneous reports of hemorrhagic stroke in patients receiving PPA for any of our conclusions about the risks of ephedrine alkaloids, and data regarding PPA is not as informative for drawing conclusions about the benefits and risks of dietary supplements containing ephedrine alkaloids as data on ephedrine. Of course, those supplements that contain meaningful amounts of PPA would pose additional serious risks expected from the use of PPA-containing products, such as hemorrhagic strokes. This adverse event can occur in healthy individuals with one dose of PPA. Reopening the docket to request comment on these data is unnecessary as we have not relied on the data for our determination in this final rule.

(Comment 25) One comment stated that l-ephedrine is both a direct and indirect-acting isomer with both alpha- and beta-agonist activity, while d-pseudoephedrine acts indirectly on both receptors. PPA, which is racemic (i.e., contains both the (+) and (-) forms of the chemical), is a direct and indirect agonist for alpha-receptors but has weaker beta-receptor activity. The comment suggested that ephedrine, pseudoephedrine, and PPA elevate blood pressure, but only l-ephedrine and d-pseudoephedrine increase heart rate. The comment cited Chua and Benrimoj (Ref. 83) stating that d-pseudoephedrine has half of the bronchodilator activity compared to l-ephedrine and one-quarter of the vasopressor effect. The comment argued that we cannot use the pharmacokinetic and toxicokinetic properties of any isomer to predict that of other ephedrine isomers. ✓

(Response) Given that *Ephedra* and other botanicals used as dietary ingredients contain a mixture of ephedrine alkaloids, and given the small database on the supposed selective effects of the isomers, we cannot draw any reassurance from the possibility that one alkaloid has more or less of an effect on the vasculature (or organ systems) than another alkaloid. Further, the reported differences in receptor binding affinity or other *in vitro* tests cannot eliminate concern about the effects of ephedrine alkaloids in humans, because there is clinical evidence that ephedrine alkaloids have important pharmacological effects (e.g., increased blood pressure, heart rate) that persist, particularly in the case of ephedrine, through at least one month of use. The REF 82 ✓ comments pointing to evidence of differences in the effects of different ephedrine alkaloids do not provide a basis to conclude that dietary supplements containing ephedrine alkaloids do not present an unreasonable risk of illness or injury.

(Comment 26) Some comments argued that the scientific literature indicates that single doses of ephedrine ~~up to 60 mg~~ generally do not increase blood pressure ~~[and doses of 60 or 90 mg of ephedrine produced only small increases in heart rate]~~ (Ref. 83). Other comments cited a handbook of intravenous drug therapy for nurses that states that ephedrine is of low toxicity. One comment stated that the scientific literature describing the effects of ephedrine in doses of 50–150 mg does not support the contention that ephedrine in dosages of 50–150 mg per day would represent a health hazard. Many comments stated that reviews of the literature and other data by independent experts reflect the scientific consensus that ephedrine alkaloids at 25 mg per dose are safe. One comment cited a clinical study of 98 elderly patients undergoing hip surgery who received 0.6mg/kg ephedrine by

loss is likely to be longer term, giving a sustained increase in blood pressure in addition to the short-term risks. If these products met prescription drug standards, then it is possible that the risks of use for weight loss could be mitigated by a physician's evaluation of the patient's medical history and appropriate monitoring during treatment. We note that manufacturers can conduct clinical investigations of ephedrine alkaloids under an IND application and can seek approval of ephedrine alkaloid-containing products as new drugs for the treatment of obesity or other diseases under a NDA if sufficient evidence is provided to support such use. It is also possible that products containing ephedrine alkaloids might not present an unreasonable risk, even without physician supervision, if they were marketed as dietary supplements for a use that results in a meaningful health benefit and that requires only temporary, episodic use to achieve the benefit. However, based on the information we have now, we believe that it is unlikely that any such non-disease use could be identified.

(Comment 30) Another 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) While caffeine would be expected to have additive effects with ephedrine alkaloids, acute administration of ephedrine alone increases blood pressure and heart rate (Ref. 37) (Ref. 47). The available evidence shows that chronic use of caffeine has no effect on blood pressure that persists beyond 2 weeks (Ref. ^{45,46} ~~46,50~~), in contrast to ephedrine, which does have a persistent effect (Boozer) (Ref. 49).

Several comments stated that pharmaceutical ephedrine is more potent than ephedrine from botanical sources because ephedrine comprises only 30 to 90 percent of the total alkaloids of the raw botanical, with the remaining portion containing potentially less potent stimulants such as pseudoephedrine. Several comments claimed that the various ephedrine alkaloids from botanical sources have a slower rate of absorption due to the plant matrix as compared to the rate of absorption for pharmaceutical ephedrine ~~(see (Ref. 43))~~. These comments stated that delayed effects diminish side effects and provide for the cardiovascular adaptation of effects, thereby diminishing cardiovascular response. One comment stated that except for absorption rate, ephedrine alkaloids from the plant have the same pharmacokinetics as pharmaceutical ephedrine (Ref. 43). Other comments note that botanical ephedrine from formulations containing whole *Ephedra* is absorbed more slowly than dietary supplements formulated with standardized extracts (Ref. 44). A few comments suggested that ephedra extract has higher neurocytotoxic (toxic effect on nerve cells) potential than synthetic ephedrine hydrochloride due to combinations of different ephedrine alkaloids or other unknown compounds found in ephedra extract that are not found in ephedrine hydrochloride (Ref. 89).

Other comments maintained that there is no difference between blood levels of ephedrine from botanical sources and ephedrine contained in OTC drugs. Comments from a State Board of Pharmacy stated that ephedrine from botanical sources is neither safer than, nor different from, pharmaceutical ephedrine. One comment objected to our including clinical studies using pharmaceutical ephedrine in our evaluation. A number of comments suggested that naturally occurring ephedrine is more potent than its synthetic counterpart. A few comments stated that the presence of varying amounts,

proportions and chemical configurations of ephedrine alkaloids in crude *Ephedra* and prepared *Ephedra* extracts, as well as the presence of unknown compounds, leads to uncertainty in dose, purity, and composition and a greater risk for adverse effects. Comments noted that this variability is not an issue for synthetic or pure isolated ephedrine alkaloids.

(Response) The data are wholly inadequate to demonstrate that any differences among forms of naturally occurring ephedrine alkaloids and synthetic ephedrine have a meaningful impact on risks to health. The overall database of clinical trials, including trials using both natural and synthetic ephedrine, does not lead to the conclusion that one form of ephedrine is safer than the other form.

We are not persuaded by any of the available evidence that ephedrine from botanical sources is materially different from ephedrine from pharmaceuticals with respect to chemistry, potency, or physiological and pharmacological effects. Chemically, any isomer with the same conformation from one source, including botanical sources, is identical to the same isomer from another source. For example, (-)-ephedrine from *Ephedra* (*Ephedra sinica* Stapf) is chemically indistinguishable from synthetic (-)-ephedrine manufactured by a pharmaceutical company.

Regarding the ephedradines, we are not aware of any evidence in the scientific literature, nor were any data provided in the comments, that indicate that these compounds are present in *Ephedra*, in other botanical sources of ephedrine alkaloids, or in extracts from these botanicals. The ephedradines are known constituents of the roots of the species *Ephedra sinica* Stapf (Ref. 90). In traditional Asian medicine, the roots and rhizome of the plant are referred to as “ma huang gen,” while the aerial parts of the plant are referred to as

“ma huang” (Ref. 3). The ephedradines are not ephedrine alkaloids. Nor are they present in the aerial parts of the plant that are used in dietary supplements. The scientific evidence, thus, does not support the opinion that the other ephedradines in the raw botanical act to modify or attenuate the physiological and pharmacological effects of the ephedrine alkaloids contained in these products.

We do not agree, therefore, that current evidence establishes that ephedrine alkaloids from botanical sources, including botanical extracts, are different from, or are any safer than, pharmaceutical ephedrine alkaloids. With regard to the comment asserting that ephedra extract is safer than pharmaceutical ephedrine because the LD₅₀ is higher for the botanical extract than the LD₅₀ for pharmaceutical ephedrine, we note that scientific views on this point differ. Another scientific reference suggests that a mixture of ephedrine alkaloids from a botanical extract may be more toxic, based on LD₅₀ calculations, than an equal amount of pharmaceutical ephedrine (Ref. 91). While there is not enough scientific evidence to draw a conclusion, we acknowledge the possibility that other components in the concentrated extracts (e.g., tannins derived from the botanical) may affect the toxicity of botanical preparations of ephedrine alkaloids (Ref. 89,92).  ✓

2. Other Safety Data

(Comment 32) Many comments cited multiple data and information sources as support for the safety of dietary supplements containing ephedrine alkaloids. These cited sources have been submitted to the docket and include the CANTOX review; RAND Report; the Ad Hoc Committee on the Safety of *And the Ad Hoc Committee on the Safety of Dietary Supplements* ^{new} Ma Huang report; *Ephedra* Education Council Expert Panel Report, and a 6-month clinical trial by Boozer et al. (2002) (Ref. 21,49,93–95). Some comments

can produce adverse health effects if intakes are excessive. However, ephedrine alkaloids are not nutrients. The CANTOX report did not include any data establishing that there is a need for ephedrine alkaloids in the diet, or that some deficiency state exists when ephedrine alkaloids are not present in the diet. Therefore, we conclude that the use of the IOM risk assessment method based on the model of a nutrient is inappropriate for the evaluation of the safety of dietary supplements containing ephedrine alkaloids.

Even if the IOM dietary reference intakes model were an appropriate risk assessment model for dietary supplements containing ephedrine alkaloids, we note that CANTOX deviated from the IOM's criteria and procedures in several important ways. For instance, the IOM report used studies published in peer-reviewed journals as the principal sources of data for its evaluations. In contrast, while CANTOX did use some publications, it also relied on abstracts and unpublished studies. For example, CANTOX cited the study by Boozer et al. as the pivotal study demonstrating the safety of dietary supplements containing ephedrine alkaloids and the establishment of the NOAEL. However, the Boozer study ^(abstract) was only available in abstract form at the time of the CANTOX review (Ref. 96). ~~Abstracts~~ ^{MOVE} Abstracts are not subject to the same rigorous peer review that full manuscripts go through. Further, abstracts do not contain sufficient information to enable a reader fully to evaluate a study's methodology or independently to interpret or verify a study's results. As a result, abstracts should not be given the same weight as the full reports of studies themselves. 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 Pharmacology Section~~ ^{V.B.1}, 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.

Indeed, of the 20 studies that CANTOX considered in identifying the NOAEL, 4 were abstracts, and 2 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 "because it connotes a level of intake that can, with high probability, be tolerated biologically by individuals; it does not imply acceptability of that level in any other sense." The IOM report also noted that "the UL is not intended to be a recommended level of intake" ((Ref. 28), ~~id.~~ at pp. 3-5). The

IOM report also stated that “the critical endpoint used to establish a UL is the adverse biological effect exhibiting the lowest NOAEL (for example, the most sensitive indicator of a nutrient or food toxicity). The derivation of a UL based on the most sensitive endpoint will ensure protection against all other adverse effects” ((Ref. 28), ~~id.~~ at p. 18). The IOM report also explained that, “When possible, the UL is based on a NOAEL, which is the highest intake (or experimental oral dose) of a nutrient at which no adverse effects have been observed in the individuals studied. This is identified for a specific circumstance in the hazard identification and dose-response assessment steps of the risk assessment” ((Ref. 28), ~~id.~~ at p. 10).

Although CANTOX defined the UL as “the maximum level of chronic daily intake of a substance judged unlikely to pose a risk to the most sensitive members of the health population,” their UL determination was based upon the “specified conditions of use,” which includes label warnings that these products not be used by many in the general population (including those under 18 years, pregnant or lactating women, and persons with certain health conditions, including those most sensitive to the effects of these products, e.g., persons with hypertension and coronary artery disease). In contrast, the IOM concept of the UL is the highest level of intake likely to pose no risk of adverse health effects to almost all individuals in the general population. Thus, the CANTOX UL is less protective than the IOM UL because it removes from its risk assessment the members of the population who would be most at risk for adverse effects of dietary supplements containing ephedrine alkaloids. (Ref. 93), ~~id.~~ p. V).

It also appears that CANTOX deviated from the IOM model in its assessment of what constituted an “adverse effect.” Although the CANTOX

report failed to define the endpoints (potential adverse effects) that were considered in the determination of a NOAEL, the report stated that “the selection of 90 mg/day is an appropriate value for a NOAEL for ephedra in light of the evidence of no significant increases in frequency of adverse effects or changes in heart rate or blood pressure at or below this level leading to cardiac arrhythmias.” Thus, it appears that CANTOX did not consider changes in heart rate or blood pressure to be “adverse effects,” although these biological effects can lead to serious adverse health consequences, such as arrhythmias and strokes. In addition, in discussing the Boozer et al. study, the CANTOX report described the statistically significant 4 mm Hg elevation in systolic blood pressure in the ephedra plus caffeine treated group as compared to the placebo group, as well as other self-reported symptoms (dry mouth, heartburn and insomnia) in the treated group, as “minimal side effects.” This choice of terminology suggests that CANTOX did not consider the well-described pharmacological effects of ephedrine alkaloids to have potentially serious adverse health effects. This difference would affect the NOAEL, which, in turn, would lead to different UL determinations. We further address the definitional issue of adverse events versus side effects later in ~~the Adverse Events~~ section ✓

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V.B.6
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We also note that CANTOX’s stated study objective, “to provide and justify a safe upper intake level for ephedrine alkaloids from ephedra used as a dietary supplement,” appears to assume that such a safe dose exists. This assumption indicates a bias towards finding a safe dose, rather than an unbiased assessment of whether any safe dose exists.

Finally, we discuss the inadequacies of the publications used by CANTOX to assess the safety of ephedrine alkaloids in ~~section xx.~~ Whatever methods ✓

V.B.2

of dietary supplements containing ephedrine alkaloids. Several comments asserted that there is a lack of serious AERs for both traditional Asian herbal products and OTC ephedrine drugs with dosages based on FDA's monograph (less than or equal to 25 mg per serving and less than or equal to 150 mg in a 24-hour period) and that these dosages are, thus, safe.

One comment maintained that the non-serious events identified by RAND are consistent with the side effects of caffeine and OTC ephedrine listed in the OTC drug review and do not pose an unreasonable risk. Other comments referred to statements made during the 1996 FDA Food Advisory Committee that there are no serious adverse effects reported with drugs containing ephedrine alkaloids within the allowable dosage range and to a February 28, 2003 FDA press release relating to ephedra that stated there are fewer AERs linked to OTC ephedrine drug products than to dietary supplements containing ephedrine alkaloids.

(Response) We do not agree that the safety of dietary supplements containing ephedrine alkaloids can be established by reference to the safety of OTC drug products containing ephedrine or pseudoephedrine, two ephedrine alkaloids currently included in OTC drug monographs.

As discussed above, all sympathomimetics may pose risks for adverse events even after a single dose. "Generally recognized as safe and effective" (GRASE) status does not mean that an OTC drug product may not cause adverse events. In fact, there have been adverse events reported to FDA concerning ephedrine- and pseudoephedrine-containing OTC drugs. There are also numerous adverse event reports for dietary supplements containing ephedrine alkaloids. The incidence and type of adverse event reports related to dietary supplements containing ephedrine alkaloids are discussed in section

V.B.6.6, which also contains our discussion on the significance of these AERs in our determination of unreasonable risk.

As part of our OTC drug review, we have determined that ephedrine and pseudoephedrine are GRASE OTC drug ingredients for certain indications. Ephedrine is GRASE for the temporary relief or symptomatic control of bronchial asthma (see 21 CFR 341.16, 341.76). Pseudoephedrine is GRASE for the temporary relief of nasal congestion due to the common cold or hay fever (allergic rhinitis) (see 21 CFR 341.20, 341.80). OTC ephedrine and pseudoephedrine drug products have been studied in controlled trials that establish their safe and effective dose for specific disease indications (labeled uses) (41 FR 38312 at 38371, 38402 to 38403, September 9, 1976) (Ref. 97,98). ✓ These OTC drug products provide health benefits when used by the population experiencing the particular disease. We note that these OTC drug products bear warnings that certain populations should not use them, and they are not risk free. However, we have determined that the demonstrated benefits for the labeled OTC drug uses outweigh their risks (see 21 CFR 330.10(a)(4)(iii)). The labeling of OTC ephedrine and pseudoephedrine drug products warns consumers not to use the products if they have heart disease, high blood pressure, thyroid disease, diabetes, or difficulty in urination due to an enlargement of the prostate gland unless directed by a doctor (21 CFR 341.76(c)(2), 341.80(c)(1)(C)). In addition, OTC ephedrine bronchodilator drug products are labeled with a warning not to use the product unless a diagnosis of asthma has been made by a doctor (21 CFR 341.76(c)(1)). Moreover, the labeling directs users not to continue to use ephedrine drug products but to seek medical assistance immediately if symptoms are not relieved within 1 hour or become worse (21 CFR 341.76(c)(5)). As discussed in the response to

comment 34, the benefits of ephedrine and pseudoephedrine drug products for disease claims are different from the benefits of dietary supplement products for non-disease claims, so it would be inappropriate to conclude based on OTC drug product information that these dietary supplements do not present an unreasonable risk. No data demonstrate that dietary supplements containing ephedrine alkaloids provide a meaningful health benefit to a particular population for any specific use and for short periods of time, as is the case for OTC ephedrine or pseudoephedrine drug products. Therefore, we have determined that the risks presented by dietary supplements containing ephedrine alkaloids (including heart attack, stroke, and death) outweigh their benefits, and that these products are adulterated regardless of what warnings are included in their labeling. We note that dietary supplements containing ephedrine alkaloids may also present other, less serious risks listed in the required warnings for OTC drugs containing ephedrine and pseudoephedrine; however, because we are removing these dietary supplement products from the market based on their cardiovascular risks, we are not addressing these other risks in this rule.

With regard to the comments that discussed safety data for OTC ephedrine bronchodilator drugs specifically, we note that the studies used to evaluate ephedrine for the treatment of asthma and those using ephedrine alkaloids for weight loss and other non-disease uses enrolled different populations and used different study designs, endpoints, and monitoring protocols. Therefore, comparisons across patient populations or indications (e.g., asthma treatment versus weight loss) for a risk benefit analysis is not justified. FDA's final rule finding ephedrine GRASE as a bronchodilator was based on the 1986¹⁹⁸⁶ 1976 recommendation of the Advisory Review Panel on OTC Cold, Cough, Allergy,

alkaloids (see 60 FR 38643 at 38644). In any event, comments about the basis and scope of our 1983 prohibition on ephedrine and caffeine combinations in OTC drug products and the 1995 ephedrine drug product proposal are not relevant to this rulemaking because we are not relying on those actions as a basis for the removal of dietary supplements containing ephedrine alkaloids.

4. Abuse and Misuse

(Comment 39) Many comments asserted that we must consider directions for use, warnings, and other labeling when making an assessment of significant or unreasonable risk. The comments stated that we cannot consider misuse or abuse of properly labeled dietary supplements. One comment urged that any evaluation of significant or unreasonable risk be based on the standards specified in the American Herbal Products Association's *Ephedra* Trade Recommendation, which recommends that dietary supplements containing ephedrine alkaloids be formulated to contain no more than 25 mg of ephedrine alkaloids per serving, that such products bear a warning statement and that directions for use limit consumption to 100 mg of ephedrine alkaloids per day (Ref. 101).

(Response) We agree that directions for use, warnings, and other labeling must be considered when making an assessment of significant or unreasonable risk. Section 402(f)(1)(A) of the act provides that whether a dietary ingredient or dietary supplement presents a significant or unreasonable risk must be evaluated "under conditions of use recommended or suggested in labeling," except that ordinary conditions of use may be considered if the labeling is silent on conditions of use. Thus, for purposes of the "significant or unreasonable risk" provision, unless no conditions of use are recommended or suggested in labeling, we must consider a dietary supplement's labeled use

rather than its actual use. We do not agree, however, that our evaluation of significant or unreasonable risk should be based on the standards specified in AHPA's *Ephedra* Trade Recommendation (Ref. 101). These standards are voluntary recommendations by a trade association and are not universally followed. We must consider all dietary supplements containing ephedrine alkaloids, not just those formulated and labeled in accordance with the *Ephedra* Trade Recommendation. In this instance, we conclude that all dietary supplements containing ephedrine alkaloids present an unreasonable risk, regardless of whether they are formulated and labeled in accordance with the *Ephedra* Trade Recommendation, based on our evaluation of the totality of the evidence and a weighing of the risks and benefits of the products. As discussed in the responses to ~~comments 64 and 65~~ ^{Section D.A.}, the presence of a warning label or of directions recommending a limit on daily consumption of ephedrine alkaloids does not sufficiently reduce the risks of dietary supplements containing ephedrine alkaloids to allow them to continue to be marketed as currently labeled or under ordinary conditions of use, and the risks of these products outweigh their benefits regardless of labeling. new

(Comment 40) Several comments compared the effects of ephedra to other sympathomimetics such as cocaine or amphetamine. Several other comments stated that while ephedrine, PPA and amphetamine are similar in chemical structure, they differ in physiological effect, and that amphetamines have much stronger reinforcing effects and a much higher liability for abuse than ephedrine. One comment stated that the subjective effects of ephedrine more closely resemble caffeine. Another comment stated that amphetamines do not have direct agonist properties, but promote release of neurotransmitters and inhibit their deactivation and reuptake. One comment from a manufacturer of

the determination we have made that dietary supplements containing ephedrine alkaloids present an unreasonable risk.

(Comment 42) Several comments stated that we cannot stop the abuse of substances by regulation. Some comments cited tobacco and alcohol as examples. Another comment stated that if we regulated products that caused injury because of their potential for abuse, then common household products, such as aerosol paint, would be banned.

(Response) Our conclusion that dietary supplements containing ephedrine alkaloids present an unreasonable risk is based not on abuse or misuse but rather on evidence supporting the presence of risks under conditions of use recommended or suggested in the labeling, or if the labeling is silent, under ordinary conditions of use. Abuse or misuse of other products is not relevant to our determination that dietary supplements containing ephedrine alkaloids present an unreasonable risk.

(Comment 43) Several comments stated the opinion that we do not appear to distinguish between dietary supplements containing ephedrine alkaloids marketed for weight loss or energy from those products marketed as alternatives to illicit street drugs or as “legal highs.”

(Response) We do not agree with these comments. Beginning with the June 4, 1997 proposed rule on dietary supplements containing ephedrine alkaloids, we have repeatedly warned industry and the public that we do not consider products marketed as street drug alternatives to be dietary supplements because they are intended for recreational purposes to affect psychological states (e.g., to get high) and are not intended to be used to augment the diet or to promote health. (See 62 FR 30678 at 30699–700) Since 1997, we have

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(Response) As discussed in the response to comment 49, we continue to believe that adverse events are underreported due to the voluntary nature of the adverse event reporting system for dietary supplements and other factors. The manufacturer comment confirms that at least some firms in the dietary supplement industry receive AERs that they do not share with us. We commissioned a study that estimated that adverse events reported to us represent less than 1 percent of all of the adverse events associated with dietary supplements (Ref. 122). Our preliminary evaluation of data purchased from the American Association of Poison Control Centers, covering the years 1997–1999, indicated more adverse events than we had received for the same years (Ref. 123). In addition, the Office of the Inspector General of the Department of Health and Human Services determined that the number of dietary supplement adverse event reports we received was significantly less than the number of dietary supplement adverse event reports received by Poison Control Centers ~~§ 9~~ of (Ref. 20).

In section ~~III.A.4.a~~ ^{VII.A.4.a}, we discuss in detail how we estimated rates of adverse event reporting for purposes of our impact analysis for this final rule.

(Comment 51) One comment stated that, despite underreporting, incomplete reports, and inadequate staff, there is no credible evidence that our reporting system makes errors in detection of adverse event signals. The comment asserted the validity of an association between AERs and risks presented by ephedrine alkaloids. The comment argued that this conclusion is confirmed by the known pharmacology of ephedrine alkaloids and the types of reports seen in ephedrine clinical trials and with drugs that have a similar pharmacological action. The comment noted that 26 percent of the reports over

loss than ephedra or ephedrine alone. The RAND report concluded that ephedrine alkaloid containing products, in combination with caffeine, resulted in a modest weight loss of approximately two pounds per month greater than that with placebo over a period of four to six months.

We also agree that this modest weight loss effect may be perceived as a benefit by consumers who seek to lose weight for non-health related purposes (e.g., to look slimmer). We do not agree, however, that these studies demonstrate the long-term weight loss necessary to provide health benefits. While the improvements in obesity/overweight and the accompanying risk factors may be demonstrated in as few as one to two months, the improvements must be maintained for years to achieve a reduction in risk (Ref. ⁶⁷126–128). We note that dietary supplements cannot be lawfully marketed for the treatment of obesity, a disease with serious health consequences. From a health perspective, the goal of weight loss is to prevent the substantial morbidity and mortality associated with overweight and obesity (Ref. ⁶⁷129,130). Obesity itself adversely impacts multiple cardiovascular risk factors, or comorbidities, including hypertension, dyslipidemia (high cholesterol), and insulin resistance with glucose intolerance. Clinical studies have demonstrated improvements in these risk markers with even modest sustained weight loss (i.e., approximately 5 to 10 percent of initial body weight). Clinical studies have also demonstrated that both the weight loss and the improvements in the comorbidities take time to accrue (i.e., months) and that, as a rule, weight is regained and the comorbidities worsened when the intervention, pharmacological or behavioral, is discontinued. Thus, interventions necessary for successful weight maintenance must be long term. As discussed in greater detail ~~below~~ in the response to comment 56, the reasonably well-documented moderate, short-

weight loss, and cited additional studies to support this view. One comment stated that 6 months is longer than the period of time recommended by FDA's Advisory Review Panel on OTC Miscellaneous Internal Drug Products with respect to evaluating weight loss ingredients used in OTC drugs. The comment stated that, by these standards, RAND's 6-month weight loss efficacy data "exceeds the scientific requirement for evaluating OTC weight loss drugs recommended by FDA's advisory panel by 3 months." Other comments stated that, from a scientific perspective, there is no reason to believe the weight loss from dietary supplements containing ephedrine alkaloids would cease after a 6-month period (Ref. ~~XI, 80~~^{70, 79}, 131). 

(Response) RAND, using the principles of evidence-based medicine, established the scope of the review and methodology used in its assessment of the currently available data. The RAND reviewers limited their evaluation to those randomized or controlled clinical trials of a minimum study duration (8 weeks) that provided adequate information, including sufficient protocol design and safety information on the basis that shorter treatment durations were insufficient to assess long-term weight loss. We believe that RAND's study selection criteria were appropriate. Further, we note that in the absence of statutory requirements for dietary supplement manufacturers to submit well-designed, long-term, placebo-controlled studies to us, the available body of well-controlled clinical data is limited. We believe that RAND appropriately screened the available data and reviewed all relevant studies and adverse event reports meeting their stated minimum standard criteria, and thus we consider the results and conclusions of this assessment valid. Exclusion of studies not directed toward weight loss or obesity was appropriate for this evaluation in

that these studies were designed to examine the efficacy of these agents for asthma and related pulmonary indications, rather than their safety.

We have reviewed the additional studies cited in the comments to support the effectiveness of dietary supplements containing ephedrine alkaloids for long-term weight loss (Ref. ^{vs 79} 60,80,131). The results of the Filozof study have been presented only in abstract form and, therefore, neither details of the protocol nor data were available for review. The Daly et al study enrolled only 24 subjects for 8 weeks in a placebo-controlled trial. After that period, 8 subjects were followed in an open label study for varying durations (1 subject was followed for 26 months). These additional studies were not evaluated in the RAND assessment because they did not meet RAND's screening criteria, and we find these studies to be either irrelevant or inadequate to change the conclusions stated in the RAND report. Therefore, we find that the Boozer 2002 study remains the longest (6-month) placebo-controlled study using ephedrine alkaloids. Consequently, we agree with RAND's conclusion that there are no studies showing an effect of dietary supplements containing ephedrine alkaloids on weight loss for more than six months.

Concerning the comment that referenced the Advisory Review Panel on OTC Miscellaneous Internal Drug Products with respect to evaluating weight loss ingredients used in OTC drugs, we note that the 1979 report of this panel was discussed in an Advance Notice of Proposed Rulemaking published in the **Federal Register** on February 26, 1982 (47 FR 8466). Based on the standard of practice at that time, the Advisory Review Panel recommended that non-monograph weight loss ingredients (i.e., those not classified as GRASE) be studied for a period of 12 weeks to demonstrate effectiveness.

with caffeine on short-term weight loss are far outweighed by the adverse effects observed in the clinical trials and the serious risks reported with the use of dietary supplements containing ephedrine alkaloids.

Several other comments, including those from an herbalist association and an herbal product manufacturer, stated that the use of these supplements, although effective, is not a sensible or healthy approach to long-term, sustainable weight management. The comment from the herbalist association also stated that obesity, with its higher risk for cardiovascular disease, is more likely to be a contraindication rather than an indication for the use of ephedra. A comment from a medical association said that NIH guidelines for the pharmacological treatment of adult obesity state that herbal preparations, including ephedra-containing products, are not recommended as part of a weight-loss program (Ref. 67).  ✓

Several comments, including one by a trade association and a medical society, while acknowledging the conclusions of the RAND report with regard to ephedrine alkaloids and weight loss, said that this effect should not be construed to imply that dietary supplements containing ephedrine alkaloids can treat diseases. One comment expressed the view that we should consistently state that obesity is a disease and, therefore, should only be treated with drugs that have been approved as safe and effective for that disease. These comments stated that use of dietary supplements to “treat” obesity is inappropriate.

(Response) As stated previously, we agree that obesity is a disease with serious health consequences; however, as some comments noted, treatment of a disease is outside the scope of the uses authorized for dietary supplements under DSHEA. Consequently, although dietary supplements containing

comment 22, on balance this trial did not show a favorable effect on cardiovascular risk factors. To the contrary, there was a statistically significant increase in heart rate in the ephedra/kola nut (i.e., herbal ephedrine alkaloids/caffeine) treated subjects compared to the control group. Moreover, 24-hour measurements of blood pressure measured by ABPM at one month showed that the ephedrine alkaloid/caffeine treated subjects had blood pressure that was approximately 4 mm Hg higher than the placebo-treated subjects for both systolic and diastolic blood pressure.

While the authors report small but statistically significant decreases in total cholesterol and ^{Low density lipoproteins} (LDL) cholesterol, the clinical significance of the net 3 mg/dl and 8 mg/dl decreases, respectively, cannot be determined from this study. In studies designed to assess modifications in cardiovascular risk factors, cholesterol changes are reported as percentage change from baseline. These data are not available from the Boozer et al. (2002) ^(Ref. 49) study.

(Comment 57) A number of comments stated that the Danish experience using ephedrine/caffeine in a prescription drug for the treatment of obesity supported the use of dietary supplements containing ephedrine alkaloids for weight loss. One comment from a manufacturer of dietary supplements containing ephedrine alkaloids shared the opinion that the effectiveness of ephedrine alkaloids “to support one’s diet” has been demonstrated in numerous studies, involving hundreds of patients in well-controlled environments, and that efficacy has also been demonstrated by extensive use data in the United States and Denmark. A comment from a medical association stated that, in Denmark, ephedrine is available to treat obesity, but only by prescription. Another comment stated that the Danish ephedrine-caffeine

product (Letigen) has been banned and withdrawn from the market because of safety issues.

(Response) We agree with the comments that the product used in Denmark, Letigen, was a prescription drug and that this drug has been withdrawn from the market for safety reasons, including serious adverse event reports documenting cardiovascular and nervous system effects (Ref. 120,121). We note that certain studies from Denmark using the ephedrine-caffeine combination found in Letigen were considered as part of the RAND report. We do not agree with the comment that numerous studies have demonstrated the effectiveness of ephedrine alkaloids to support weight loss for the treatment of obesity, as discussed previously. The use of dietary supplements containing ephedrine alkaloids has been shown to produce a small, short-term weight loss, but no studies showing long-term weight loss with accompanying benefits to health have been conducted. In any case, if botanical ephedrine alkaloid products could be shown effective in long-term treatment of obesity or for long-term weight loss in people who are not obese, they would need to be marketed as prescription drugs and meet the standards of safety and effectiveness legally mandated for such products because physician supervision would be necessary to adequately mitigate the risks of using these products continuously in the long term.

2. Enhancement of Athletic Performance

(Comment 58) Several comments discussed the effects of ephedrine alkaloids on athletic performance. One comment noted that, while RAND states that ephedrine is a good surrogate for evaluation of dietary supplements containing ephedrine alkaloids, RAND does not make this extrapolation for athletic performance. Many other comments stated that there are few data to

support the use of synthetic ephedrine alkaloids, and no data to support the use of dietary supplements containing ephedrine alkaloids to enhance athletic performance. Therefore, these comments do not consider the enhancement of athletic performance to be an appropriate use for dietary supplements containing ephedrine alkaloids. According to some comments, RAND concluded that there are insufficient data to support use for enhancement of athletic performance. One comment asserted that any effect on athletic performance is more likely due to the caffeine in ephedrine-caffeine dietary supplements. According to another comment, the few studies that have assessed the effect of ephedrine for this use support a modest effect of ephedrine plus caffeine on very short-term (1–2 hours after a single dose) athletic performance in a highly selected, physically fit population, but no studies have assessed the effect of dietary supplements containing ephedrine alkaloids.

(Response) We generally agree with these comments. The RAND report provides the most comprehensive, currently available review of efficacy studies for ephedrine alkaloid containing products, focusing on two popular uses of these products—athletic performance and weight loss (see section V.C.1). (Note that the RAND report did not consider the effectiveness data for ephedrine alkaloid containing products marketed as drugs for other uses, such as to treat asthma, or for other dietary supplement uses of such products.) The effect of synthetic ephedrine on athletic performance was assessed in seven studies that were reviewed in the RAND report. The RAND report noted that the effects of ephedrine on exercise performance were most often studied acutely (e.g., one to two hours after a single dose)(Ref. 21,22). The RAND report could identify no studies that assessed the effect of dietary supplements

containing ephedrine alkaloids on athletic performance. While the RAND report found that existing data supported a modest effect of synthetic ephedrine alkaloid containing products plus caffeine on athletic performance enhancement in healthy males in the very short term, no data support a sustained improvement in athletic performance over any significant time period. In these studies, the performance enhancement effect was demonstrated only with a combination of synthetic ephedrine and caffeine, not with ephedrine alone. Therefore, since the available evidence does not indicate that ephedrine itself enhances athletic performance, there is no need to address the issue as to whether ephedrine is a good surrogate for ephedra in evaluating athletic performance enhancement with the use of dietary supplements containing ephedrine alkaloids.

We determined that certain labeling claims made by manufacturers of dietary supplements containing ephedrine alkaloids for athletic performance enhancement were unsubstantiated in light of the findings in the RAND report. These claims were the subject of warning letters sent to various manufacturers in February and March 2003 (available at <http://www.fda.gov/bbs/topics/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} ~~any adequately~~ substantiated benefit _{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

including looking at the statute's text, structure, and legislative history." *Chevron v. Federal Energy Regulatory Commission*, 193 F.Supp.2d 54, 67 (D.C. Cir. 2002). Section 402(f)(1)(A) of the Act states that a dietary supplement is adulterated if it presents a significant or unreasonable risk of illness or injury under the conditions of use recommended or suggested in labeling, or, if the labeling is silent, under ordinary conditions of use. The plain meaning of the statute is the starting point of statutory interpretation. ^{(See} 2A SUTHERLAND STATUTORY CONSTRUCTION 81 (5th ed. 1992).) The words "significant" and "unreasonable" have two different meanings. "Significant" involves an evaluation of risk alone. The plain meaning of "unreasonable," on the other hand, connotes comparison of the risks and benefits of the product. A risk could be significant but reasonable if the benefits were great enough to outweigh the risks. That "unreasonable risk" entails a balancing test in which the benefits of the product or activity are weighed against its dangers is well-established in tort law. (See PROSSER AND KEETON ON THE LAW OF TORTS, §31, at 173 (5th ed. 1984).)

^{Stet} In assessing whether Congress has clearly spoken to the question at issue, a court "should not confine itself to examining a particular statutory provision in isolation. Rather, it must place the provision in context, interpreting the statute to create a symmetrical and coherent regulatory scheme." *FDA v. Brown and Williamson Tobacco*, 529 U.S. 120 (2000). The term "unreasonable risk" is used in other provisions of the act, e.g., in the provisions related to medical devices. In the medical device classification provisions, Class III devices are distinguished from Class I and Class II devices in part because they present a "potential unreasonable risk of injury or illness." The legislative history of the device provisions provides some indication of how Congress intended FDA

to interpret the term “unreasonable risk in this context. The House Committee Report states: “the requirement that a risk be unreasonable contemplates a balancing of the possibility that illness or injury will occur against the benefits of use.” H.R. Rep. No. 853, 94th Cong., 2d Sess. 16–17 (1976). Therefore, “unreasonable risk” in the context of classification of medical devices is properly interpreted to require a risk-benefit calculus. There is nothing in the provisions of the act dealing with dietary with dietary supplements, or the legislative history thereof, that would suggest that FDA should interpret the term “unreasonable risk” in the context of dietary supplements differently than it does in the context of medical devices.

An interpretation of unreasonable risk as entailing a balancing of the risks and benefits of the product is also consistent with the interpretation of other similar statutory provisions outside the act. The Toxic Substances Control Act contains an “unreasonable risk” standard, and legislative history indicates that Congress intended that this standard be evaluated through a balancing test. E.g., H.R. Rep. No. 94–1341, 94th Cong., 2d Sess. 13–14 (1976). Indeed, it is difficult to construct an alternative formulation for the phrase “unreasonable risk.”

Based upon the plain meaning of “unreasonable risk,” the judicial interpretation of that phrase, and legislative history interpreting “unreasonable risk” in other contexts, including the device provisions of the act and other statutes, we conclude that Congress unambiguously intended that an assessment of “unreasonable risk” in the dietary supplement context should entail a risk-benefit analysis.

In the alternative, if a court were to find that Congress has not directly spoken to the issue of whether “unreasonable risk” in the dietary supplement

substantial risk of illness or injury” states that “[A]ctual proof of deception or injury to an individual is [not] required.” Section 516 of the act (21 U.S.C. 360f); H.R. Rep. No. 853, 94th Cong., 2d Sess. 18 (1976). Case law on medical device classification also supports that we need not have causal evidence of harm. See *Lake v. FDA*, 1989 WL 71554 (E.D. Pa.) (upholding FDA’s finding of unreasonable risk where the risks were unknown and the benefits unproven). Therefore, we conclude that Congress has spoken clearly and unambiguously that proof of causation is not required to show that a dietary supplement presents an “unreasonable risk” under section 402(f)(1)(A) of the act. ✓

Our interpretation is also consistent with other statutes that regulate public health risks, most notably TSCA. 15 U.S.C. § 2601 *et seq.* (1976). TSCA authorizes the Environmental Protection Agency (EPA) to place restrictions on chemical substances if it finds that “there is a reasonable basis to conclude that the [chemical substance] presents or will present an unreasonable risk of injury to health or the environment.” *Id.* § 2605(a). The legislative history of this provision states, “This standard for taking action recognizes that factual certainty respecting the existence of an unreasonable risk of a particular harm may not be possible and the bill does not require it. Further, regulatory action may be taken even though there are uncertainties as to the threshold levels of causation.” H.R. Rep. No. 94-1341, 94th Cong., 2d Sess. 25 (1976).

(Comment 62) Several comments stated that any FDA regulatory approach to dietary supplements containing ephedrine alkaloids must consider *both* risks and benefits, and moreover, that we should determine, based on scientific evidence, a risk-benefit ratio for assessing their safety. These comments suggested that, if we were to set a break-even point, a decision matrix should

clinical trials. Other references submitted by these comments included (Ref. 19,34,42,133-~~136~~). 

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 1980–94, and that in 1997 the Centers for Disease Control and Prevention (CDC) attributed 42 percent of deaths to conditions that typically result from obesity. One comment stated that the risks due to obesity are a greater danger than the rare incidences of stroke or heart attacks attributed to dietary supplements containing ephedrine alkaloids.

Other comments concluded that dietary supplements containing ephedrine alkaloids do not present an unreasonable risk because the risks do not outweigh the benefits. They argued that while the benefits of dietary supplements containing ephedrine alkaloids are substantiated, the adverse events reported are either mild, anecdotal, or unsubstantiated and not scientifically valid. Some comments cited the RAND report to support the benefit of ephedrine alkaloids for short-term weight loss and the lack of adverse effects in clinical trials. The comments assert that only a speculative

in section V. C.2, the available evidence regarding a possible benefit from these products for enhancing athletic performance is further limited: the supporting evidence all comes from studies in which synthetic ephedrine and caffeine in combination were administered to healthy males, and the modest effects shown were in the very short term only. Even if one could disregard all the gaps in the scientific evidence and assume that ephedra has the same effect on athletic performance as synthetic ephedrine in combination with caffeine, we do not consider a modest, temporary enhancement of certain aspects of athletic performance to be a benefit sufficient to outweigh the risks of dietary supplements containing ephedrine alkaloids. Therefore, we conclude that the use of dietary supplements containing ephedrine alkaloids to enhance athletic performance for any duration of use present an unreasonable risk.

iii "Eased Breathing" and Other Uses. We have long recognized the legitimate short-term oral use of sympathomimetics, such as ephedrine, in OTC bronchodilator drug products. These products are marketed for those who have been diagnosed with asthma by a physician. The products are GRASE when formulated and labeled in accordance with the requirements of the final monograph for OTC bronchodilators (21 CFR Part 341). Mandatory warnings include advising the consumer not to use the product unless diagnosed as having asthma by a doctor and not to use the product if suffering from heart disease or high blood pressure.

We are aware that there are dietary supplements containing ephedrine alkaloids that are marketed for uses other than weight loss or athletic performance enhancement, such as "eased breathing," "better breathing," "feel better," "feel more alert," "energized." By contrast to the monograph-compliant OTC bronchodilators, and as discussed above in section ~~xx~~, we have

V.B.3

diseases. Although we could require labeling for dietary supplements containing ephedrine alkaloids to limit the duration of use, among other things, currently there are no data that demonstrate that dietary supplements containing ephedrine alkaloids provide a benefit to a particular population when used temporarily or episodically (in contrast to OTC ephedrine and pseudoephedrine products for disease uses).

3. Conclusion

Multiple studies demonstrate that dietary supplements containing ephedrine alkaloids, like other sympathomimetics, raise blood pressure and increase heart rate. These products expose users to several risks, including the consequences of a sustained increase in blood pressure (e.g. serious illnesses or injuries that include stroke and heart attack that can result in death) and increased morbidity and mortality from worsened heart failure and pro-arrhythmic effects. Although the pro-arrhythmic effects of these products typically occur only in susceptible individuals, the long-term risks from elevated blood pressure can occur even in nonsusceptible, healthy individuals. ~~These risks are not outweighed by the available, limited evidence of benefit for short-term weight loss and the lack of evidence for athletic performance, increased energy or alertness, or better breathing. Nor do the benefits outweigh the risks under ordinary conditions of use, in the absence of suggested or recommended conditions of use in product labeling.~~ On the other hand, we have determined that there are benefits from the use of OTC and prescription drug products containing ephedrine alkaloids in certain populations for certain disease indications that outweigh their risks.

As with other sympathomimetics, the risks posed by dietary supplements containing ephedrine alkaloids for continuous, long-term use cannot be

adequately mitigated without physician supervision. Temporary, episodic use can be justified only if a known or reasonably likely benefit outweighs the known and reasonably likely risks. Similar to OTC single ingredient ephedrine products, dietary supplements containing ephedrine alkaloids could theoretically be marketed without physician supervision for a very temporary, episodic use if there were adequate evidence that the use resulted in a benefit sufficient to outweigh the risks of these products. However, we are currently unaware of any such use, and our experience with ephedrine and pseudoephedrine OTC drug products suggests that such benefits will be demonstrable only for disease uses. Therefore, we conclude that dietary supplements containing ephedrine alkaloids present an unreasonable risk of illness or injury under conditions of use recommended or suggested in labeling or under ordinary conditions of use, if the labeling does not suggest or recommend conditions of use.

VI. Why We Conclude that Other Restrictions Would Not Adequately Protect Consumers from the Risks Presented by Dietary Supplements Containing Ephedrine Alkaloids

We considered several regulatory alternatives to this final rule. As discussed in section ^{I.C}~~xx~~, we issued a proposed rule in 1997 that would have placed various restrictions on dietary supplements containing ephedrine alkaloids. ~~As discussed in section I.B of this document,~~ ^{new} Most of the proposed restrictions were withdrawn in 2000; only the proposed prohibition on combining ephedrine alkaloids with other stimulant ingredients and the proposed warning statement (as modified in FDA's March 2003 **Federal Register** notice (68 FR 10417)) remain. As discussed below, we have reached the conclusion that those restrictions are inadequate to protect public health.

E. Nonbinding Guidance

(Comment 69) Several other comments recommended the issuance of nonbinding guidance providing notice to marketers as to which dietary supplements containing ephedrine alkaloids would most likely be the subject of FDA enforcement. One comment argued that a guidance document would conform to our good guidance practices (21 C.F.R. 10.115) and provide guidance to the dietary supplement industry as to a level of ephedrine alkaloids that can be used in their products with some confidence that such products will not be subject to regulatory action. In arguing for a guidance document and against a regulation, the comment said that a federal regulation is only appropriate and necessary to protect the public health when safe use of a product cannot be ensured absent such a regulation; the comment maintained that we have not made this showing. One comment stated that the major dietary supplement industry trade associations could exhort industry compliance to guidelines issued by us or by the trade associations.

(Response) We disagree that nonbinding guidance would be an effective substitute for this rulemaking. As stated above, several industry trade associations have established policies concerning the formulation and labeling of dietary supplements containing ephedrine alkaloids. These policies are non-binding and manufacturers and distributors are under no obligation to comply. Moreover, as discussed ~~above~~ in the response³⁹²¹ to comment~~s~~⁶⁷, guidance on labeling or product formulation, even if adhered to, would be insufficient to protect consumers from the risks posed by dietary supplements containing ephedrine alkaloids.

of obesity); failed to present data that industry believed to be relevant to the evaluation (e.g., number of units of products sold during the period of time the AERs were received, data regarding whether a cause and effect relationship existed between dietary supplements containing ephedrine alkaloids and the 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 Working Group and Food Advisory Committee meetings were unfair. The comments cited several reasons, including: 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 Working Group or Food Advisory Committee (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 "Policy and Guidance Handbook for FDA Advisory Committees" (1994). We ^(Ref. 1B) 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 supplement industry. The consumer and industry representatives represented the views of consumers and industry throughout the meeting and made recommendations to us. All FDA-prepared materials to be considered by the Committees were sent to all members of the Committees, including the dietary supplement industry representatives, prior to the meeting.

Third, the Committees' meetings provided a forum for public discussion. 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. During the Committees' meetings, we provided over two hours of public hearing time, which is twice the time required by our regulations, 21 C.F.R. § 14.29 (a).

Thus, contrary to the comments' assertions, we provided ample opportunity for public participation in the meetings. The public hearings were conducted prior to the Committees' deliberations so that comments made by interested parties could be considered by the Committees in making their recommendations.

VIII. Analysis of Impacts

A. Benefit-Cost Analysis

Introduction

We have examined the economic implications of this final rule as required by Executive Order 12866 (E.O. 12866). Executive Order 12866 directs us to

certainty.” If other possible causes could not be excluded, then the report classified the cases as possible sentinel events. This level of certainty is unusually high in the context of identifying a public health risk.

We also disagree that we should use only clinical studies when estimating the number of adverse events. In addition, we disagree with the comments that stated that because clinical studies find baseline rates for stroke and major cardiac events in excess of 1 per 1,000, the existing clinical evidence is sufficient to detect adverse events associated with ephedrine alkaloids. The clinical studies reviewed by RAND were not large enough to distinguish between effects of ephedrine alkaloids and the ordinary variance around the baseline. We, therefore, do not agree that existing clinical studies are sufficiently large to detect additional adverse events associated with ephedra or ephedrine. As discussed in section V.³ of this document, the scientific evidence identifies the risks presented by dietary supplements containing ephedrine alkaloids. For example, a six-month clinical study examining the efficacy and safety of ephedrine alkaloids for the treatment of obesity found a statistically significant association between treatment with ephedrine alkaloids and higher blood pressure compared to placebo (Ref. 49). Higher blood pressure tends to increase the likelihood of cardiovascular disease. Thus, the clinical evidence establishes a potential mechanism leading from the use of dietary supplements containing ephedrine alkaloids to the occurrence of serious adverse effects.

We link the findings from this clinical study and the well-known pharmacological effects of ephedrine alkaloids to adverse events to establish the likelihood that at least some adverse events reported to be associated with the use of dietary supplements containing ephedrine alkaloids were in fact

90 percent to 100 percent for sentinel events and 50 percent to 100 percent for possible sentinel events.

Second Assumption: 100 percent of the sentinel and possible sentinel events that were caused by dietary supplements that we suspect contained ephedrine alkaloids involved dietary supplements that did, in fact, contain ephedrine alkaloids.

(Comment 75) Other comments addressed the second assumption. One comment reported that an industry review of the 920 AERs in the docket found that more than 123, or 13 percent, involved products for which there was no indication that the product contained ephedrine alkaloids. One comment was from a firm that claimed it had informed us during the Food Advisory Committee (FAC) meetings that nearly 25 percent of the AERs that involved their products involved products that did not, in fact, contain ephedrine alkaloids. ?
previously asked?

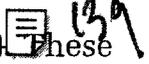
(Response) One of the criteria that RAND used to identify sentinel and possible sentinel events was documentation that the person that suffered the adverse event had consumed a dietary supplement containing ephedra within 24 hours prior to the adverse event. The assumption in the proposed rule that 80 percent of the AERs involved products that contained ephedrine alkaloids applied to the set of AERs used in that analysis. RAND has documented that all of the sentinel and possible sentinel events it reviewed involved products containing ephedrine alkaloids. Documentation of the presence of ephedrine alkaloids varied from case to case, and included blood tests of the person who suffered the adverse event, chemical analysis of capsules, and labeling of the products consumed. RAND did not consider self-reports alone to be sufficient documentation for sentinel and possible sentinel events. Because we use the

RAND study as the basis for the analysis of this final rule, the 80 percent assumption is no longer relevant. In the analysis of this final rule, we assume that 100 percent of the AERs involved products that contained ephedrine alkaloids.

Third assumption: AERs represented 10 percent of the actual number of adverse events.

(Comment 76) Some comments argued that our assumption of a 10 percent reporting rate was too low. Some comments argued that people are more likely to over-report than underreport adverse events involving dietary supplements containing ephedrine alkaloids for various reasons, including FDA's public statements and media coverage of this issue. One comment argued that people are more likely to over-report than under-report serious adverse events such as heart attack, stroke, seizure, psychotic events, and death, because people tend to consider any temporal connection equivalent to a causal connection. However, this comment suggested that people probably underreport minor adverse events. Some comments noted that the AERs that we discussed in the 1997 proposed rule appeared to arrive in discrete groups as though in response to inciting events, such as FDA press releases. One comment noted that, of the 22 AERs in the docket that involved their products, we received two-thirds of those AERs within one week of our April 1996 press release, and we received the other one-third over a much longer period of 30 months. Some comments suggested that the 10 percent assumption might be appropriate for passive reporting systems, but argued that the reporting system that we used to generate the AERs was not passive because both the Texas Department of Health and FDA took various steps to solicit AERs. Two comments discussed estimates of reporting rates for a passive adverse event reporting system in

clear
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Britain. One comment estimated the reporting rate for serious adverse events at 50 percent. Another comment estimated the same rate at 10 percent. Both comments estimated that the system had a much smaller reporting rate of 2 percent to 4 percent for non-serious adverse events. Some comments noted that we assumed a 50 percent reporting rate in our report on Eosinophilia-Myalgia Syndrome, which was an outbreak level event (Ref. 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 over-report 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 non-serious adverse events. This comment argued that the reporting rate for serious adverse events is probably higher than for non-serious 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 the adverse events under consideration and the level of media coverage suggest that the reporting rate may be 10 percent or higher. The assumed 100 percent reporting rate generates a lower bound number of adverse events. We selected 50 percent as an intermediate number. We used a 10 percent reporting rate in our summary statements to simplify the presentation of the results and because 10 percent reporting appears to be a reasonable point estimate, taking into account the seriousness and media coverage of these adverse events and the estimated reporting rates of 1 percent or lower for adverse events involving drugs (Ref. 32,139). The 10 percent reporting rate applies to serious events only, and incorporates the fact that a report of a serious adverse event had to fulfill the RAND criteria in order to be included as a sentinel or possible sentinel event. We did not consider non-sentinel events in the analysis, as explained below.

Valuing reductions in adverse events

(Comment 77) Some comments addressed the values that we placed on eliminating various types of adverse events in the analysis of the proposed rule. One comment objected to the value of \$5 million that we placed on ~~reducing health risks such that one would estimate~~ one fewer fatality per year across the affected population, which is sometimes called the value of a statistical life. This comment described this value as the value of an average life and argued that this figure is unrealistic because the average person does not have \$5 million. ✓ new

(Response) In its guidelines on performing economic analysis of federal regulations under E.O. 12866, OMB noted that the term “statistical life” can lead to some confusion. It pointed out that this term refers to the sum of risk reductions expected in a population, as expressed in the following example: If the annual risk of death is reduced by one in a million for each of two million people, that represents two “statistical lives” saved per year (two million x one in one million = two). If the annual risk of death is reduced by one in 10 million for each of 20 million people, that also represents two statistical lives saved (Ref. 140). Similarly, the estimated value of a statistical life (VSL) is based on the willingness to pay for relatively small reductions in the risk of premature death for many people summed across a population. The individual risk management decisions on which we base estimates of the VSL must reflect the budget constraints of those individuals making those decisions. However, the resulting VSL need not reflect the budget constraints of the average person. We have revised the VSL in this analysis to a range of \$5 million to \$6.5 million to reflect the latest estimates of this figure (⁶⁸~~60~~ FR 41433–41506) ^(July 11, 2003).

In addition, we have revised our method of estimating the values of avoiding the other health endpoints. For non-fatal myocardial infarction (MI), we used the same procedure that we used in our analysis of the proposed rule on trans fatty acids (^{(SIC) 604} ~~60~~ ^{Nov. 17, 1999} FR 62772). That method was based on estimating the sum of the medical costs, the cost of functional disability, and the cost of pain and suffering. This method assumes that someone suffering a non-fatal MI will have functional disability or pain and suffering or both in every year after the year following the MI. We estimated the loss per year to be 0.2 quality adjusted life years (QALYs) every year of life following the MI. We did not include

refers to an improvement to health and is not synonymous to the “benefits” that we mention in our risk-benefit analysis for purposes of determining that these products present an unreasonable risk of illness or injury; “health benefits” are a type of “benefit” we consider when making an unreasonable risk determination.) Our full conceptual model of benefits is as follows: (net change in risk from the reduction in intake of ephedrine alkaloids x value per unit change in risk) + (net change in risk from substitute products and activity x value per unit change in risk) + (net change in risk from weight gain x value per unit change in risk) + (any net change in risk from the small impact on wealth from the cost of substitute products or activity x value per unit change in risk).

However, we do not have sufficient information to estimate all elements of this model. In the analysis of the proposed rule, we noted one article that found that a product a firm had reformulated to remove ephedrine alkaloids had lost approximately 33 percent of its previous sales (Ref. 145). Since that time, a media report discussed another reformulated product that had greater sales than the original product (Ref. 146). Therefore, we estimate that from two-thirds to all of the consumers of these supplements would probably switch to other dietary supplements that firms market for the same purposes as dietary supplements containing ephedrine alkaloids. This implies that between one-third and none of the consumers of these products would switch to entirely different types of weight loss or performance enhancing substitutes.

Some manufacturers have already reformulated dietary supplements so that products that had contained ephedrine alkaloids now contain alternative ingredients. Some of these reformulated products contain Citrus aurantium L., which is a source of synephrine, and caffeine, sometimes in the form of green

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tea extract. Synephrine is a sympathomimetic agent, and these agents are a class of compounds that also includes ephedrine alkaloids. A number of other potential herbal sources of sympathomimetics probably exist. These ingredients may pose risks that are similar to those of ephedra. If consumers switched to substitute products containing these ingredients, similar health risks might be expected as those with products containing ephedrine alkaloids. Some other ingredients that have been reported in reformulated products include cocoa beans, yerba mate, cinnamon twig, and galangal.

The estimated none to one-third of the consumers of dietary supplements containing ephedrine alkaloids who would switch to products other than other dietary supplements might switch to alternatives that carry either health risks or benefits. Some of those who consumed these supplements for weight loss may seek medical care to obtain prescription weight loss medications or for weight loss surgery. However, only some of these consumers would qualify for these medical treatments. These treatments would carry health risks that might be equal to, or greater than, the risks of ephedrine alkaloids. Only the risks that remain after accounting for the management of risk under physician supervision would be relevant in this context. In addition, these treatments may be more expensive than dietary supplements. The resulting relatively small reductions in the overall wealth of those who switch to more expensive alternatives could also generate small countervailing health risks because ^{those} ~~they~~ consumers have less disposable income to spend on other risk-reducing activities.

Other consumers interested in weight loss may switch to meal replacements or other diet products rather than seek medical treatment. Other consumers might choose to do nothing and simply forego the weight loss they may have obtained with ephedra products. This foregone weight loss could,

in theory, generate health costs. The lack of health benefits from the weight loss associated with the use of these products, however, implies that these health costs, if any, would be negligible. Finally, some consumers might choose to reduce their caloric intake or increase their caloric output through additional exercise. These consumers would obtain additional health benefits beyond eliminating the risk of adverse events associated with dietary supplements containing ephedrine alkaloids. Those who consume supplements containing ephedrine alkaloids to enhance their athletic performance and who do not switch to other dietary supplements marketed for that purpose might switch to other stimulants, including black market products containing ephedrine alkaloids or methamphetamines. These products would pose health risks equal to or greater than those of currently marketed dietary supplements containing ephedrine alkaloids.

We have insufficient information to quantify the effects of switching to alternative weight loss or athletic performance enhancing products or activities, or to quantify the health costs associated with the absence of weight loss that might be achieved using dietary supplements containing ephedrine alkaloids.

Risks of Certain Dietary Supplements Containing Ephedrine Alkaloids ~~from the Market~~

(Comment 81) A number of comments suggested that certain dietary supplements containing ephedrine alkaloids do not pose any health risks. These comments addressed this point in the context of exempting certain products from the proposed warning statement. However, these comments are also relevant to the issue of exempting certain products from a regulation

reformulation. The FDA reformulation cost model does not address costs for a reformulation time of six months, so we extrapolated the costs based on the proportionate change in cost that would result from halving the reformulation time from twelve months to twenty-four months. Under that extrapolation, we estimate that reformulation costs for a six-month reformulation period would be \$10 million to \$100 million. We annualize these estimated costs over 20 years at an interest rate of 3 percent to convert these one-time costs to a yearly cost of \$1 million to \$7 million. Annualizing these costs over 20 years at an interest rate of 7 percent gives an annual cost of \$1 million to \$9 million.

We summarize the annual costs of this option in Table 3. We compare the benefits and costs of this option in Table 4. To obtain the higher bound estimate of net benefits, we start with the higher bound estimate of benefits and subtract the lower bound estimates of costs. To obtain the lower bound estimate of net benefits, we start with the lower bound estimate of costs and subtract the higher bound estimate of costs. If consumer behavior already incorporates health risks, then utility costs would already be net of health benefits. In that case, the net impact of this rule is simply the total costs.

TABLE 3.—ANNUAL COSTS OF OPTION TWO (REMOVING DIETARY SUPPLEMENT CONTAINING EPHEDRINE ALKALOIDS FROM THE MARKET)

Type of Cost	Cost (rounded to \$ millions)
Utility Losses for Consumers	\$6 to \$81
Product Reformulation	\$1 to \$9

TABLE 4.—ANNUAL SOCIAL BENEFITS AND COSTS OF OPTION TWO (REMOVING DIETARY SUPPLEMENT CONTAINING EPHEDRINE ALKALOIDS FROM THE MARKET)

Type of Benefit or Cost	Benefit or Cost (rounded to \$ millions)
Health Benefits (for 10 percent reporting rate) \$43 to \$132	
Cost of Utility Losses for Consumers \$6 to \$81	
Cost of Product Reformulation \$1 to \$9	
Net Effect (if consumer behavior does not already incorporate health risks) -\$47 to -\$129	
Net Effect (if consumer behavior already incorporates health risks) -\$90 to -\$7	

→ more numbers to this column

that the profit rate is 5 percent of sales, removing dietary supplements containing ephedrine alkaloids from the market would generate accounting profit losses of \$0 to \$1~~2~~³ million per year. We classify this impact as a transfer and not a social cost because removing dietary supplements containing ephedrine alkaloids from the market would increase the profits of firms that produce and distribute substitute products. If these other firms also have an average profit rate of five percent of sales, then the profit gained by these companies would also equal \$0 to \$13 million per year.

In addition to causing a potential reduction in profits for firms currently producing dietary supplements containing ephedrine alkaloids, removing dietary supplements containing ephedrine alkaloids from the market might also generate some countervailing transfers through the elimination of insurance costs and lawsuits associated with products containing ephedrine alkaloids. Eliminating legal fees and court costs would also generate social benefits. Of course, if reformulated products were eventually found to pose health risks comparable to those found for ephedra-based products, then these effects (i.e., the elimination of insurance and legal costs) would eventually decrease to zero. A recent press report found that ephedra manufacturers or distributors have settled 33 cases since 1994 and that an additional 42 cases were pending (Ref. 152). This represents 75 cases over nine years, or about 8 cases per year. Recent awards for cases that have gone to court have ranged from \$2.5 million to \$13 million (Ref. 152,153). The figures reported in the media for cases that were settled out of court were considerably lower. One such case was settled out of court for \$25,000 (Ref. 152). If removing dietary supplements containing ephedrine alkaloids from the market eliminated 8 cases per year, then it would decrease transfer payments from firms to

statements because existing warnings do not alert consumers to avoid taking multiple products containing ephedrine alkaloids at the same time.

(Response) To address these comments, we reviewed and compared the labels of forty dietary supplements containing ephedrine alkaloids that we collected between March 20 and May 30, 2001, ~~and also compared the number of adverse reports received during the period January 2000 to January 2004 as warning labels appeared on certain dietary supplements.~~ (Ref. 157a) ¹⁵⁷  All of the product labels bore some sort of warning statement. Most warning statements had many of the same basic elements as the proposed warning statement. For example, most existing warnings listed various conditions under which consumers should not take the product, various conditions under which consumers should see a health care provider before taking the product, and side effects or symptoms that should lead consumers to consult with a health care provider. However, the specific content of the various elements varied quite a bit both among existing warning statements and between existing warning statements and the proposed warning statement. Some elements of the proposed warning statement were common in existing warning statements; other elements were less common. For example, none of the existing product labels carried a principal display panel (PDP) warning statement. In contrast, most product labels carried some sort of warning for people who had previously experienced heart problems. In addition, parts of some existing warnings were more strongly worded than the corresponding parts of the proposed warning. In other cases, parts of the proposed warning were more strongly worded than the corresponding parts of existing labels. Our label comparison did not support the notion that the proposed warning statement would have no effect because it was identical to existing warning statements.

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The comparison did suggest that the proposed warning statement is similar in many respects to existing warning statements, and that the proposed warning statement might not reduce adverse events very much. This result is consistent with the assumption that the proposed warning statement might eliminate between 0 and 15 percent of adverse events.

(Comment 85) Some comments argued that the proposed warning statement would be ineffective because some States already require warning statements, and the presence of multiple warning statements would confuse consumers.

(Response) Multiple warning statements might reduce the impact of the proposed warning statement. However, ~~a combination of multiple warnings~~ ^{many different} statements ~~might be more effective than relying on one or a few warning statements.~~ The comments did not provide sufficient information to enable us to revise our estimate of the effectiveness of the proposed warning statement based on the possibility that some products might face multiple labeling requirements.

b. *Revised Benefit Estimates.* When we revise the analysis as described above, we obtain the estimated benefits shown in Table 5. The assumption underlying the table is that the proposed warning statement would cause some proportion of consumers to incorporate the risks from dietary supplements containing ephedrine alkaloids into their demand for these products. Some proportion of those consumers (0 to 15 percent) would cease using those products, which would reduce the number of adverse events by a like percentage. The benefits would therefore be some percentage (between 0 and 15 percent) of the benefits of removing dietary supplements containing ephedrine alkaloids from the market. The results presented in Table 5 apply

to every year after the first year. Benefits for the first year would be lower because our proposed rule would have allowed firms up to six months to comply with the warning statement requirements. We do not know the actual rate at which firms would come into compliance during the initial six months after publication of a rule finalizing the proposed warning statement requirements. To simplify the analysis, we assume that it would take all firms six months to comply with such a rule. Under this assumption, the benefits in the first year would be half those of every year after the first year. In the summary of regulating options and Table 8, we use the range \$0 to \$20 million for annual benefits (excluding the first year) because it is inconsistent with the presentation of the other options.

TABLE 5.—ANNUAL BENEFITS OF OPTION THREE (REQUIRE THE 2003 PROPOSED WARNING STATEMENT) BASED ON ELIMINATING 0 TO 15 PERCENT OF THE SENTINEL AND POSSIBLE SENTINEL EVENTS

Type	Number	QALY Loss Per Case	Medical Costs per Case
Death	0.0 to 0.2	NA (used VSL)	\$25,742
MI (heart attack)	0.0 to 0.2	0.29	\$30,586
CVA (stroke)	0.0 to 0.3	0.2	\$20,898
Other Cardiovascular (e.g. Cardiomyopathy, Ventricular Tachycardia)	0.0	0.29	\$30,586
Other Neurological (e.g. Transient Ischemic Attack)	0.0	minimal	\$13,212
Seizure	0.0 to 0.1	minimal	\$11,812
Psychiatric	0.0 to 0.2	minimal	\$6,927

Table 6.—Annual Benefits of Option Three (Require the 2003 Proposed Warning Statement) Based on Alternative Assumptions of Reporting Rates, rounded to \$ millions

Value of Avoiding Fatal Cases and QALY Losses	Adverse Event Reporting Rate		
	10 percent	50 percent	100 percent
\$ per fatal case = \$5 million\$ per QALY = \$100,000 \$0 to \$11 \$0 to \$2 \$0 to \$1.			
\$ per fatal case = \$6.5 million\$ per QALY = \$100,000 \$0 to \$14 \$0 to \$3 \$0 to \$1.			
\$ per fatal case = \$5 million\$ per QALY = \$300,000 \$0 to \$14 \$0 to \$3 \$0 to \$1.			
\$ per fatal case = \$6.5 million\$ per QALY = \$300,000 \$0 to \$17 \$0 to \$3 \$0 to \$2.			
\$ per fatal case = \$6.5 million\$ per QALY = \$500,000 \$0 to \$20 \$0 to \$4 \$0 to \$2.			

leads to fix

c. Costs of Requiring the 2003 Proposed Warning Statement

Label Costs

(Comment 86) Some comments said that the proposed PDP or non-PDP warning statements are too long to fit on the labels of most dietary supplement products. One comment noted that firms package many “traditional style extracts” in containers that have a maximum label size of 1.75 x 3.75 inches,

ingredient lists: ephedra, ephedra extract, ephedra herb, *Ephedra sinica* Stapf., ma huang, ma huang extract, ma huang herb, ma huang concentrate, or ma huang herb extract (Ref. 158).¹⁵⁹ In the absence of other information, we assume that the cost of changing the labels of these products would be about 2 percent of the cost of changing all dietary supplement product labels. Therefore, we estimate that the one-time cost of changing the labels of dietary supplements containing ephedrine alkaloids is \$3 million to \$6 million. Annualizing this cost over twenty years at 3 percent gives an annual cost that rounds to \$0 million per year; that is, less than \$500,000 per year. Annualizing this cost over twenty years at 7 per cent gives an annual cost of \$0 million to \$1 million.

Risks of Substitutes/Absence of Weight Loss

(Comment 87) One comment noted that the proposed warning statement would instruct consumers not to take dietary supplements containing ephedrine alkaloids before or during strenuous exercise. This comment argued that this element of the warning statement could harm consumers by inhibiting weight loss because exercise is an essential component of a weight loss program.

(Response) As we discussed under Option Two of this section, we have insufficient information to estimate countervailing health effects such as the health risks generated by the use of substitute products or by the reduction or elimination of weight loss benefits. However, for this option, we have calculated benefits as a range of \$0 to \$20 million. This range is consistent with the existence of countervailing health risks from the source suggested by this comment.

d. Effective Date

already understand and voluntarily accept the risks posed by these products, to an annual net social benefit of \$125 million, if there are no countervailing health risks and consumers do not already understand and accept the known and potential risks.

TABLE 8.—SUMMARY OF OPTIONS (ROUNDED TO \$ MILLIONS)

Excluded Comments w/ all Tables (see Table 2)

Option	Annual Cost	Annual Benefit	Net
1. Take No New Regulatory Action (baseline)	\$0	\$0	\$0
2a. Remove dietary supplements containing ephedrine alkaloids from the market (if consumer behavior does not already incorporate risk)	\$7 to \$90	\$43 to \$132	-\$47 to \$125
2b. Remove dietary supplements containing ephedrine alkaloids from the market (if consumer behavior already incorporates risk)	\$7 to \$90	\$0	-\$90 to -\$7
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 Info. or take some action other than removal or warning statements	unknown	unknown	unknown

C. 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). ¹⁰ 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

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proposed rule. This database listed 30 firms associated with 48 dietary supplement products containing ephedrine alkaloids (Ref. 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 contract to FDA (Ref. 159). This database had size information for only a few of the 30 firms that we identified as relevant from the first database. Therefore, we estimated the number of small firms based on the percentage of all dietary supplement firms in the database that would qualify as small firms. The Small Business Administration (SBA) publishes definitions of small businesses by the North American Industry Classification System (NAICS) code. The firms in the database fell into the following NAICS codes: 311222 Soybean Processing, 311920 Coffee and Tea Manufacturing, 325188 All Other Basic Inorganic Chemical Manufacturing, 325199 All Other Basic Organic Chemical Manufacturing, 325411 Medicinal and Botanical Manufacturing, 325412 Pharmaceutical Preparation Manufacturing. SBA defines small businesses in these NAICS codes based on a maximum number of employees, as follows: 311222 and 311920—no more than 500 employees; 325411 and 325412—no more than 750 employees; and 325188 and 325199—no more than 1000 employees. The database of firms listed 1,566 individual plants and 146 parent companies. Essentially all individual plants qualified as small businesses (98 percent under a maximum of 500 employees and 100 percent under a maximum of 1,000 employees). However, approximately 12 percent of the individual plants were associated with parent companies, and only about half of the parent companies qualified as small businesses (53 percent under a maximum of 500 employees and 58 percent under a maximum of 1,000 employees). Based on this information, we estimated that about 94 percent of

X. Paperwork Reduction Act

This final rule contains no collections of information. Therefore, clearance by OMB under the Paperwork Reduction Act of 1995 is not required.

XI. Federalism

We have analyzed this final rule in accordance with the principles set forth in Executive Order (E.O.) 13132. FDA has determined that the rule has a preemptive effect on State law. Section 4(a) of the Executive order requires agencies to “construe * * * a Federal Statute to preempt State law only where the statute contains an express preemption provision or there is some other clear evidence that the Congress intended preemption of State law, or where the exercise of State authority conflicts with the exercise of Federal authority under the Federal statute.” Section 402(f)(1)(A) of the act states that a dietary supplement or dietary ingredient shall be considered adulterated if it presents a significant or unreasonable risk of illness or injury under conditions of use recommended or suggested in the product’s labeling. If no conditions of use are suggested or recommended in the product’s labeling, the dietary supplement or dietary ingredient is considered to be adulterated if it presents a significant or unreasonable risk of illness or injury under ordinary conditions of use. We have concluded that dietary supplements containing ephedrine alkaloids present an unreasonable risk and are therefore adulterated under section 402(f)(1)(A) of the act.

Section 402(f)(1)(A) of the act does not expressly preempt State or local laws. Therefore, under section 4(b) of E.O. 13132, we are to construe our rulemaking authority as authorizing preemption of State law by rulemaking “only when the exercise of State authority directly conflicts with the exercise of Federal authority under the Federal statute or there is clear evidence to

published the June 4, 1997, proposed rule. Such consultation and notice was not possible because we published the proposed rule in the **Federal Register** on June 4, 1997, and E.O. 13132 was not signed until August 4, 1999. The Office of Management and Budget^{OMB}'s guidance for implementing E.O. 13132 states that, when a final rule may have been promulgated as a proposed rule before August 4, 1999, such that the intergovernmental consultation process had not occurred as called for by E.O. 13132, the agency's certification "should so state" (see Memorandum for Heads of Executive Departments and Agencies, and Independent Regulatory Agencies, dated October 28, 1999)^(Ref 16)). Thus, we certify that the intergovernmental consultation process described in section 4(d) of E.O. 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, E.O. 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 (see 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 (see 68 FR at 10417, 10419–10420). Although the March 5, 2003, notice did not contain a separate Federalism analysis, we believe that States were aware of the March 5, 2003, notice because at least five State or local governments or legislators submitted