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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 112⁹

[Docket No. 1995N-0304]

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REVISIONS

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

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

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

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

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

1. Introduction
 2. Regulatory Options
 3. Summary of Conclusions
 4. Option One—Take No New Regulatory Action
 5. Option Two—Remove Dietary Supplements Containing Ephedrine Alkaloids from the Market
 6. Option Three—Require the 2003 Proposed Warning Statement
 - a. Benefits of requiring the 2003 proposed warning statement
 7. Option Four—Require the proposed warning statement, but modify it or require it only on certain products
 8. Option Five—Generate additional information or take some other action other than removing dietary supplements containing ephedrine alkaloids from the market or requiring warning statements
- B. Benefit-Cost Analysis: Summary
- C. Small Entity Analysis

IX. Environmental Impact

X. Paperwork Reduction Act

XI. Federalism

I. Introduction

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

We conclude that dietary supplements containing ephedrine alkaloids are adulterated under section 402(f)(1)(A) (21 U.S.C. 342(f)(1)(A)) of the act because they present an unreasonable risk of illness or injury under the conditions of use recommended or suggested in labeling, or if no conditions of use are suggested or recommended in labeling, under ordinary conditions of use.

Dietary supplements containing ephedrine alkaloids are most often used for weight loss, energy, or to enhance athletic performance.

By its plain language, section 402(f)(1)(A)[#] of the act requires evidence of “significant or unreasonable risk” of illness or injury. There is no requirement that there be evidence proving that the product has caused actual harm to specific individuals, only that scientific evidence supports the existence of risk. The Government’s burden of proof for “unreasonable risk” is met when a product’s risks outweigh its benefits in light of the claims and directions for use in the product’s labeling or, if the labeling is silent, under ordinary conditions of use. “Unreasonable risk,” thus, represents a relative weighing of the product’s known and reasonably likely risks against its known and reasonably likely benefits. In the absence of a sufficient benefit, the presence of even a relatively small risk of an important adverse health effect to a user may be unreasonable. Because it is not reasonable to conclude that a product is too risky in the absence of any significant evidence, some weight of evidence of risk is required to meet this standard. For example, isolated adverse events alone might not be expected to constitute substantiation of risk, but adverse event reports combined with pharmacological and other clinical evidence might be expected to do so. SK

In considering whether dietary supplements containing ephedrine alkaloids present an unreasonable risk, we considered evidence from three principal sources: (1) The well-known, scientifically established pharmacology of ephedrine alkaloids; (2) peer-reviewed scientific literature on the effects of ephedrine alkaloids; and (3) the adverse events (including published case reports) reported to have occurred following consumption of dietary supplements containing ephedrine alkaloids.

supplements containing ephedrine alkaloids is consistent with the

Commission's advice.

In September 1998, the U.S. General Accounting Office (GAO) began a study on FDA's June 1997 proposal. GAO's work culminated in the issuance of a July 1999 report (Ref. 17). GAO concluded that the evidence supported concern that ephedrine alkaloid-containing supplements can cause serious health problems and it recommended further data collection and review. At the same time, GAO criticized FDA's reliance on adverse event reports (AERs) as the basis for the proposed restrictions on dosage, frequency and duration of use.

In the **Federal Register** of April 3, 2000 (65 FR 17474, April 3, 2000), we withdrew parts of the June 1997 proposal. More specifically, we withdrew the proposed finding that a dietary supplement is adulterated if it contains 8 mg or more of ephedrine alkaloids per serving, or if its labeling suggests or recommends conditions of use that would result in the intake of 8 mg or more in a 6-hour period or a total daily intake of 24 mg or more of ephedrine alkaloids; the proposed compliance procedures (regarding the analytical method FDA would use to determine the level of ephedrine alkaloids in a dietary supplement); the proposed label statement "Do not use this product for more than 7 days;" the proposed prohibition on labeling claims for uses that encourage long-term intake; and the proposed label statement to accompany claims for short-term uses ("Taking more than the recommended serving may cause heart attack, stroke, seizure, or death.").

We stated in our 2000 partial withdrawal of the June ¹⁹⁹⁷ proposal that we continued to have a public health concern about the use of dietary supplements containing ephedrine alkaloids and that we would continue to

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monitor and provide appropriate followup on adverse events associated with the use of these products. We also stated that withdrawal of certain provisions of the proposed rule did not limit our discretion to initiate enforcement actions with respect to dietary supplements containing ephedrine alkaloids.

On the same day as the 2000 partial withdrawal of the June 1997 proposal, we announced the availability of certain documents to update the administrative docket of the proposed rule (65 FR 17509, April 3, 2000). The documents consisted of additional information about some of the 270 adverse event reports (AERs) received by FDA between February and September 1997. In a separate **Federal Register** notice also issued on April 3, 2000, we announced the availability of additional AERs and related information received after publication of the proposed rule. The additional information included the analyses of these new AERs by experts both inside and outside the agency; review of labels of products associated 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 U.S. Department of Health and Human Services (HHS) 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 June 1997 proposal 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).

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literature does not support an effect of ephedrine alone on athletic performance, and there were no clinical trials on the effects of dietary supplements containing botanical ephedrine alkaloids on athletic performance. One of the studies reviewed by RAND, a study by Boozer, et al. (2002), though frequently relied on by the dietary supplement industry to demonstrate the safety of ephedrine alkaloids, raised additional concerns about the effects of dietary supplements containing ephedrine alkaloids on blood pressure. This evidence, discussed in section V.B of this document, added significantly to the evidence suggesting that dietary supplements containing ephedrine alkaloids as currently marketed are associated with unreasonable safety risks.

At about the same time as we published the March ²⁰⁰³ notice, we issued SR warning letters to 26 firms for making unsubstantiated claims concerning the use of dietary supplements containing ephedrine alkaloids to enhance athletic performance. We also issued warning letters to firms promoting dietary supplements containing ephedrine alkaloids as alternatives to illicit street drugs.

In July 2003, GAO testified at a House Subcommittee hearing on issues relating to dietary supplements containing ephedrine alkaloids. GAO's testimony discussed and updated some of its findings from its prior 1999 report on dietary supplements containing ephedrine alkaloids (Ref. 23). The testimony provided new information, including an evaluation of Metabolife International's records of health-related calls from consumers of Metabolife 356 (Ref. 24). GAO noted that the types of adverse events identified in the health-related call records from Metabolife International were consistent with the types of adverse events reported to us, as well as with the scientifically documented physiological effects of ephedrine alkaloids. GAO also noted that

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. 1995N-0304, 2000N-1200, and 2001P-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 comments were received from persons who had, or who knew persons who had, suffered adverse events or who were reporting adverse events associated with the use of an ephedrine alkaloid-containing dietary supplement. The remaining comments included those submitted by medical professionals, scientists, medical or scientific associations, State or local health departments, government agencies, members of Congress, dietary supplement manufacturers, traditional Asian medicine practitioners and associations, dietary supplement industry trade associations, public health associations, and consumer groups.

The form letters, while not submitting substantive evidence or analyses, expressed strong views about our regulation of these products. Most of these letters opposed further federal regulation of dietary supplements containing

(Response) Although we agree that the terms ephedrine, pseudoephedrine, and PPA refer to different chemical entities, we disagree with the rest of the comment and its conclusions. The term “ephedrine alkaloids” refers to a class of naturally occurring compounds structurally related to ephedrine, and the term has been used in that manner in the scientific literature (Refs. 25 and 26). We chose this particular term, rather than several alternatives, such as “*Ephedra* bases” and “ephedrine type alkaloids,” to limit the scope of the June 1997 proposal to those compounds that are natural constituents of the aerial parts of the *Ephedra* plant or other botanical sources of ephedrine and related alkaloids. We also defined the term by listing the six principal natural alkaloids in the June 1997 proposal and other FDA documents (Refs. 6 and 27). The ephedrine alkaloids in botanicals include l-ephedrine, d-pseudoephedrine, l-norephedrine, l-methylephedrine, d-norpseudoephedrine, d-methylpseudoephedrine, and minor related alkaloids. All of these 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 VI. ^{row B.1} of this document, we recognize ^{species} 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.

products are therefore adulterated under section 402(f)(1)(A) of the act. We are using our general rulemaking authority to issue regulations for the efficient enforcement of the act (section 701(a) of the act) to issue a regulation applying the standard in the context of a particular category of dietary supplements—those that contain botanical ephedrine alkaloids. We are not required to issue a separate rule or guidance defining the 402(f)(1)(A) standard before issuing such a regulation. Similarly, lack of a regulation or guidance defining the standard neither prevents us from taking enforcement action against dietary supplements that present an “unreasonable risk,” nor is it new legislation necessary for us to interpret the meaning of “unreasonable risk.” If Congress has clearly spoken to a question of statutory interpretation, the agency charged with administering the statute must implement the unambiguous intent of Congress (“*Chevron* step one”) (*Chevron U.S.A., Inc. v. Natural Resource Defense Council*, 467 U.S. 837, 842–43 (1984)). If a statute is silent or ambiguous on the question, however, the agency may interpret the ambiguous provision (“*Chevron* step two”) *Id.* at 843–844. ^{delete 741.} When such administrative interpretations are made through rulemaking, they will be upheld as long as they are reasonable and consistent with the statute’s purpose and legislative history (*Christensen v. Harris County*, 529 U.S. 576, 587 (2000); *Chevron U.S.A., Inc. v. FERC*, 193 F.Supp.2d 54, 68 (D.D.C. 2002)). As discussed in the response to comment 59 in section V.D.1 of this document, we have concluded under *Chevron* step one that the phrase “unreasonable risk” clearly directs FDA to conduct a risk-benefit analysis. Even if a court were to find that phrase ambiguous, however, our interpretation is reasonable under *Chevron* step two.

(Response) We are not addressing these comments because we have chosen to proceed under section 402(f)(1)(A) of the act ✓

(Comment 15) One industry comment stressed that comments to the June 1997 proposal may not be used to authorize other final regulations. The comment expressed concern that comments to a proposed warning statement would be used as a basis for another FDA action to regulate these supplements.

(Response) We disagree with this comment. FDA may issue this final regulation based on a finding that dietary supplements containing ephedrine alkaloids are adulterated because they present an unreasonable risk under section 402(f)(1)(A) of the act. APA requires agencies to provide the public with notice and an opportunity for comment before issuing a new regulation (5 U.S.C. 553(b) and (c)). In keeping with this requirement, a final rule may differ from a proposed rule if the final rule is a “logical outgrowth” of a proposed rule (*Small Refiner Lead Phase-Down Task Force v. EPA*, 705 F.2d 506, 547 (D.C. Cir. 1983)). The inquiry into whether a final rule is a logical outgrowth of the proposed rule is often stated as whether the regulated party “should have anticipated that such a requirement might be imposed” (*Small Refiner*, 705 F.2d at 549). Agencies “undoubtedly have authority to promulgate a final rule that differs in some particulars from its proposed rule* * * [a] contrary rule would lead to the absurdity that * * * the agency can learn from the comments on its proposals only at the peril of starting a new procedural round of commentary” (*Small Refiner*, 705 F.2d at 546-⁵47 (quoting *International Harvester Co. v. Ruckelshaus*, 478 F.2d 615, 632 n.51 (D.C. Cir.1973))). The D.C. Circuit has also stated: “The APA notice requirement is satisfied if the notice fairly apprises interested person of the subjects and issues the agency is considering; the notice need not specifically identify “every

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precise proposal which [the agency] may adopt as a final rule” (Chemical ~~Ass’n~~ Waste Mfrs. v. EPA, 870 F.2d 177, 203 (5th Cir. 1989) (quoting *United Steelworkers of Am. v. Schuylkill Metals*, 828 F.2d 314, 317 (5th Cir. 1987) (internal citations omitted))).

Our June ^y 1997 proposal, along with our March 5, 2003 **Federal Register** notice, provided a sufficient basis to allow the public to anticipate our actions in this final rule. Through our proposed actions on dietary supplements containing ephedrine alkaloids, the public was properly notified of the possibility that we would find such products to be adulterated under section 402(f)(1)(A) of the act. In fact, our March 2003 notice (68 FR 10417) specifically asked for comment on whether dietary supplements containing ephedrine alkaloids present a significant or unreasonable risk under section 402(f)(1)(A) of the act. We also sought comment on new evidence concerning the safety of dietary supplements containing ephedrine alkaloids (68 FR 10417 at 10420). In addition, the restriction on ephedrine alkaloid/stimulant combinations proposed in 1997, which was unaffected by the 2000 partial withdrawal proposal, was based in part on a finding of adulteration under section 402(f)(1)(A) of the act (62 FR 30678 at 30696). Though we did not specifically propose to codify a finding of adulteration based on significant or unreasonable risk in the March 2003 notice, it was clear that we were contemplating the possibility that dietary supplements containing ephedrine alkaloids were adulterated under section 402(f)(1)(A) of the act. Courts have upheld final rules that contained new elements when the public was made aware that the agency was contemplating such a change (See *Chem. Mfrs. Ass’n.*, 870 F.2d 202–203). Furthermore, we received several comments regarding the possibility of a finding that all dietary supplements containing

ephedrine alkaloids would be deemed adulterated under section 402(f)(1)(A) of the act. Though not determinative of logical outgrowth in and of themselves, comments on the issue are evidence that the public received adequate notice of our final rule (*Shell Oil v. EPA*, 950 F.2d 741, 757 (D.C. Cir. 1991)). Based upon our explicit request for comments on the adulteration issue in our March 2003 notice, our reference to the section 402(f)(1)(A) of the act adulteration standard as a basis for our June 1997 proposal, and the fact that a number of parties commented on whether dietary supplements containing ephedrine alkaloids present a significant or unreasonable risk, there was adequate notice to the public of our actions in this final rule.

(Comment 16) Several comments cited language in section 402(f)(1) of the act providing that courts must review any determination under section 402(f)(1) of the act *de novo* and further stated that we would not get judicial deference in any court review. The comments argued that, under this provision, it would make no difference whether we brought our case initially in court or whether we proceeded through rulemaking that was subsequently challenged in court. One trade association noted that such *de novo* review is a novel approach in that usually a court would just review the administrative record.

(Response) Section 402(f)(1) of the act states that a court will decide any issue under that paragraph on a *de novo* basis. We agree that the *de novo* standard of review applies to our factual findings under section 402(f)(1) of the act, but do not agree that it applies to our conclusion under *Chevron U.S.A., Inc.* that “unreasonable risk” means a risk-benefit analysis (see section V.D.1 of this document). This interpretation of the de novo provision of section 402(f)(1) of the act is consistent with case law on the *Toxic Substances Control*

Act (TSCA), which contains an unreasonable risk standard coupled with a “substantial evidence” standard of review, analogous to the act’s unreasonable risk standard coupled with a *de novo* standard of review. In *Chemical Manufacturers Association v. EPA*, 859 F.2d 977 (D.C. Cir. 1988), the D.C. Circuit distinguished the EPA’s legal interpretation of unreasonable risk, which received deference under *Chevron U.S.A., Inc. v. Natural Resources Defence Council*, 467 U.S. 837 (1984), from its burden of showing with “substantial evidence” in the record that it has met the standard. The court stated: “This fairly rigorous standard of record review should not * * * be confused with the substantive statutory standard * * * ” (859 F.2d at 992). Thus, the court in *Chem. Mfrs. Ass’n.* held that the “substantial evidence” standard of record review applied to the factual basis of EPA’s decision but not to its interpretation of the statutory standard. In applying *Chevron U.S.A., Inc.*, we have concluded that Congress unambiguously intended that unreasonable risk entails a risk-benefit calculus. If a court were to find the phrase “unreasonable risk” ambiguous, however, our interpretation of unreasonable risk as meaning a risk-benefit calculus should receive *Chevron U.S.A., Inc.* deference, like EPA’s interpretation of the statutory standard in *Chem. Mfrs. Ass’n.* The requirement for *de novo* review should be applied only to the factual basis of FDA’s determination.

Regardless of which standard applies, however, our determination that dietary supplements containing ephedrine alkaloids present an unreasonable risk under section 402(f)(1)(A) of the act should be sustained by a court. Our conclusion that “unreasonable risk” entails a risk-benefit analysis is consistent with the express intent of Congress. The scientific evidence regarding the pharmacology of products containing ephedrine alkaloids, clinical studies

proceeding is a rulemaking, not a civil action being referred to the Department of Justice, and therefore the 10-day notice requirement does not apply.

(Comment 18) One industry comment stated that the stringent 30-day timeframe allowed for comments in response to the March 2003 notice did not provide the industry with a fair opportunity to review the administrative record and fairly respond to “any alleged new evidence and analyses” by FDA. This comment urged us to allow for a comment period of 180 days. The comment stated that this procedural lapse would render the entire rulemaking process arbitrary and capricious.

(Response) We disagree with this comment. We believe that the 30-day comment period on the March 2003 notice provided interested persons with an adequate opportunity for review and comment. The information placed in the public docket at that time was limited, consisting of the RAND report plus six recent studies. APA requires only that an agency “give interested persons an opportunity to participate in the rulemaking through submission of written data, views, or arguments * * *” This opportunity to participate is all that the APA requires. There is no statutory requirement concerning how many days we must allow for comment, nor is there a requirement that we extend the comment period at the request of an interested person (See *Phillips Petroleum Co. v. EPA*, 803 F.2d 545, 559 (10th Cir. 1986)). Moreover, given that we first opened a docket on the issue of dietary supplements containing ephedrine alkaloids in 1995 and sought comments on this issue several times between then and 2003 (see section I.C of this document), there has been ample opportunity for all those interested to submit information and views.

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 19 of this document). 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 postmarketing 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 (Refs. 29a, 29, and 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 time, and on a population-wide basis, result in thousands of adverse health events.

In making a determination, we consider studies using closely related products. In considering the risks of a product, such as dietary supplements

because the benefits that may result from use of these products are outweighed by the risks associated with such use (See discussion in section V.D of this document). Because of the nature of these risks, we do not believe it is appropriate to delay action until further clinical studies can be conducted to evaluate the safety of dietary supplements containing ephedrine alkaloids in the general population. We would, however, support the conduct of clinical investigations (carried out under the Investigational New Drug (IND) regulations with careful screening to exclude subjects at risk and careful safety monitoring during the trials) that examine the safety and efficacy of ephedrine alkaloids, with or without caffeine, as drugs such as for the treatment of obesity (See 21 CFR part 312).

(Comment 20) Two comments stated that there is an accepted scientific methodology for determining whether, and at what level, a food additive, dietary ingredient, OTC or prescription drug, or biologic may be hazardous to human health. The stated components of this methodology include reviews of the following reports: (1) The existing scientific literature on the substance, to determine what is known about the substance's risk, particularly at the levels to be used in a product; (2) clinical studies involving the substance; (3) available animal studies on the substance and, if necessary, the conduct of additional studies; and (4) adverse event reports caused by the substance. In addition, the methodology includes a determination of whether individuals who consume the products suffer from a statistically significantly greater number of adverse (or beneficial) events than those who do not. One comment stated that the absence of premarket approval authority for dietary supplements does not preclude reliance on traditional methods of evaluating safety when making a decision about levels that are not safe.

we intend to meet our obligations under the Data Quality Act and the implementing Office of Management and Budget (OMB) guidelines, states that we are committed to ensuring that our regulatory decisions are based on objective information and notes our commitment to using the best available science conducted in accordance with sound and objective scientific practices, including peer reviewed science and supporting studies when available. This comment also cited the Center for Food Safety and Applied Nutrition's report "Initiation and Conduct of All ^{left single quote}Major' Risk Assessments within a Risk Analysis Framework" (<http://www.cfsan.fda.gov/~dms/rafw-toc.html>), which similarly stresses the importance of data quality and scientific objectivity in regulatory decisionmaking. Finally, this comment suggested that in evaluating the safety of dietary supplements containing ephedrine alkaloids, we should apply a rigorous scientific standard such as that used to evaluate whether a new drug application (NDA) should be approved or whether a health claim should be authorized under the significant scientific agreement standard (See §§ 314.125 and 314.126) (NDAs); Guidance for Industry: Significant Scientific Agreement in the Review of Health Claims for Conventional Foods and Dietary Supplements (<http://www.cfsan.fda.gov/~dms/ssaguide.html>) (health claims).

(Response) We agree that we have an obligation to base regulatory assessments, including our regulatory assessment of the safety of dietary supplements containing ephedrine alkaloids, on sound science. We have spent a great deal of time and effort compiling and evaluating the best available scientific evidence relevant to this rulemaking, and our decision is based on a careful, objective analysis of the most current information, including peer reviewed studies. In considering whether dietary supplements containing ephedrine alkaloids present an unreasonable risk, we considered evidence

from three principal sources: (1) the well-known, scientifically established pharmacology of ephedrine alkaloids; (2) peer-reviewed scientific literature on the effects of ephedrine alkaloids; and (3) the adverse events (including published case reports) reported to have occurred following consumption of dietary supplements containing ephedrine alkaloids. We believe that this final rule, and the data considered, are consistent with the principles set forth in the Data Quality Act and related guidances cited in the comments. We do not agree, however, that we should apply the same standard of scientific proof to a determination of adulteration under section 402(f)(1)(A) of the act, the “significant or unreasonable risk” provision, as we would apply to a decision whether to approve an NDA or authorize a health claim under other provisions of the act. Although our decision on dietary supplements containing ephedrine alkaloids must be based on sound science, that decision is not subject to, and need not meet, the very specific evidentiary requirements set out in the new drug and health claim provisions of the act (See 21 U.S.C. 355(d) and 21 U.S.C. 343(r)(3)(B)(i)).

B. What Are the Known and Reasonably Likely Risks Presented by Dietary Supplements Containing Ephedrine Alkaloids?

1. Pharmacology

We have reviewed numerous studies and other data related to the safety of dietary supplements containing ephedrine alkaloids. Evidence about the pharmacology of ephedrine alkaloids—as well as other evidence in the docket—shows that these products present a risk of serious adverse health effects. Information submitted to the docket in an effort to establish the safety of these products is inadequate to rebut the evidence of risk.

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

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

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

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

The extremely high prevalence of diagnosed and undiagnosed hypertension in the U.S. population and the likelihood that blood pressure in obese patients is already elevated make the 4 mm Hg effect shown by the Boozer et al. (2002) study (Ref. 47) one of great concern. Reductions in blood pressure of this magnitude (i.e., around 4 mm Hg diastolic or systolic) are clearly associated with substantial long-term reductions in the occurrence of heart attack, stroke and death, as seen in meta-analyses of antihypertensive drug trials (Refs. 55 and 56). While these trials were conducted in patients with hypertension, increasing blood pressure in any population, even in individuals with "normal" blood pressure, will increase the risk of cardiovascular disease (Ref. 29).

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

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 proposal (Refs. 36 and 67 through 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

at least 100 patients to detect a difference from placebo of around 4 to 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 to 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 (Refs. 29a, 29, and 54), as can ephedrine's sympathomimetic effects in people with

otherwise healthy individuals who may have a genetically predetermined sensitivity to ephedrine alkaloids or other sympathomimetic agents. Other comments asserted that warning labels are ineffective because serious adverse events have occurred after the initial or first few uses.

(Response) We generally agree with the comments. Warning labels may be beneficial when people are able to identify the risk factors about which they are being warned. As explained in section V.B.3 of this document, OTC drug products containing ephedrine or pseudoephedrine bear warnings that they should not be used by certain populations. Despite the identified risks of these products, we have determined that the demonstrated health benefits for the labeled OTC drug uses outweigh their risks for certain temporary, episodic disease uses when appropriate warnings are contained in the product labeling. While dietary supplements containing ephedrine alkaloids present the same risks, there are no health benefits for the labeled uses sufficient to outweigh their risks (See discussion in section ^SV.C and V.D of this document). A more detailed discussion on why a warning label would be insufficient to make the risks of dietary supplements containing ephedrine alkaloids reasonable appears in section VI.A of this document.

(Comment 29) A number of comments indicated that ephedrine alkaloids could only be used safely under the supervision of a health professional or that products containing ephedrine alkaloids should be restricted to prescription use only. Reasons given for these opinions included the potential for interactions between dietary supplements containing ephedrine alkaloids and caffeine or other commonly available products (predominantly drugs) that might not be identified by the typical consumer. Other comments stated that consumers could not self diagnose many of the conditions where the use of

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 nondisease 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 (Refs. 37 and 47). The available evidence shows that chronic use of caffeine has no effect on blood pressure that persists beyond 2 weeks (Refs. 45 and 46), in contrast to ephedrine, which does have a persistent effect (Boozer) (Ref. 47).

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clinical trial by Boozer et al. (2002) (Refs. 21, 49, 93, and 95). Some comments also claimed that the toxicological database supports clinical evidence of safety; that no serious adverse events have been reported in controlled clinical trials using products containing ephedrine alkaloids for weight loss, and that few or no serious adverse events have been reported to manufacturers of dietary supplements containing ephedrine alkaloids.

One trade association commented that a valid and quantitative scientific process is needed to identify intakes and conditions of use that do not cause significant or unreasonable risk, and urged us to adopt scientific conclusions based on the CANTOX risk assessment, which was based on methods developed by the Institute of Medicine (IOM) (Ref. 28). A number of comments argued that the results of the CANTOX review established that dietary supplements containing ephedrine alkaloids are safe when used in accordance with the industry standard.

One comment stated that the methods employed by CANTOX were not appropriate for use in evaluating the safety of dietary supplements containing ephedrine alkaloids. Several comments stated that there are no data that establish that ephedrine alkaloids are an ordinary component of food, that there is a need for ephedrine alkaloids in the diet, or that some deficiency state exists when ephedrine alkaloids are not a normal component of the diet.

(Response) We do not agree with the methodology or conclusions of the risk assessment performed by CANTOX. The CANTOX review, sponsored by an industry trade group, was a quantitative risk assessment that used IOM methods to determine a safe upper level (called the No Observed Adverse Effect Level (NOAEL)) for botanical ephedrine alkaloids as used in dietary supplements. We believe that this review cannot be used to establish a NOAEL

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 section V.B.6. of this document.

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.

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of ephedrine alkaloids and therefore are potentially more dangerous than dietary supplements that contain these substances at lower levels.

(Response) Our decision in this rulemaking to treat dietary supplements that contain ephedrine alkaloids differently from OTC drugs that contain ephedrine or pseudoephedrine is not arbitrary or capricious. Our decision is based on differences in the intended uses of these products, as well as differences in the scientific evidence available to support the risk-benefit ratio for the products. The risk-benefit ratio is dependent on several factors, including the product's intended use, the product's benefits, if any, and the availability of adequate measures to control risk.

As discussed previously, dietary supplements containing ephedrine alkaloids present an unreasonable risk of illness or injury because their risks outweigh their benefits. Like dietary supplements containing ephedrine alkaloids, OTC drug products containing ephedrine or pseudoephedrine have risks related to these ingredients. However, unlike dietary supplements, such OTC drug products have demonstrated benefits in the treatment and mitigation of disease. Through the OTC drug review process, we have determined that drug products containing ephedrine are ~~generally recognized as safe and effective~~ (GRASE) for OTC use as a bronchodilator for the temporary relief or symptomatic control of bronchial asthma (See §§ 341.16 and 341.76), and that drug products containing pseudoephedrine are GRASE for OTC use as a nasal decongestant for the temporary relief of nasal congestion due to the common cold or hay fever (allergic rhinitis) (See §§ 341.20 and 341.80). Based on controlled clinical investigations (See § 330.10(a)(4)(ii)), we have determined that the benefits associated with the use of OTC drug products containing ephedrine and pseudoephedrine for these disease indications outweigh the

risks and justify the use of these products despite their risks. However, such uses for disease mitigation and treatment are beyond the scope of permissible dietary supplement uses.

Moreover, we do not agree that dietary supplements containing ephedrine alkaloids are safer than OTC drugs containing ephedrine or pseudoephedrine based on the relative doses of ephedrine alkaloids in these products. We consider an OTC drug product's safety in the context of its conditions of use (See § 330.10(a)(4)(i)). OTC drugs containing ephedrine and pseudoephedrine are marketed to persons with specific disease conditions or symptoms for temporary, episodic relief. In fact, OTC ephedrine bronchodilator drug products are required to bear a warning limiting the use of these products to persons who have been diagnosed with asthma by a doctor (See § 341.76(c)(1)). Additionally, although drug products containing ephedrine and pseudoephedrine are permitted to be marketed OTC at specific doses, these doses have been determined based on the specific indications of these drugs. As previously discussed, the indications and benefits applicable to OTC drugs containing ephedrine and pseudoephedrine do not apply to dietary supplements. Thus, the safety of dietary supplements containing ephedrine alkaloids cannot be established merely by showing that the level of ephedrine alkaloids in these products falls within or under the dose ranges permitted for OTC drug products. Furthermore, these dietary supplements contain several ephedrine alkaloids, making it difficult to draw any conclusions about benefits from studies using OTC drug products that contain a single ephedrine alkaloid.

(Comment 35) Several comments pointed out that we have concluded that the ephedrine levels permitted in OTC drugs are generally recognized as safe. Other comments maintained that the long-term marketing and favorable safety

discussed in section V.B.6.e of this document , 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 §§ 341.16 and 341.76). Pseudoephedrine is GRASE for the temporary relief of nasal congestion due to the common cold or hay fever (allergic rhinitis) (See §§ 341.20 and 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 and 38402 to 38403, September 9, 1976) (Refs. 97 and 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 § 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 (§§ 341.76(c)(2) and 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 (§ 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

alkaloids for weight loss, as well as other uses, and have discussed our analysis and conclusions regarding weight loss in section V.C.1 of this document.

(Comment 37) Numerous comments asserted that herbal medicines, including ephedra, have a favorable safety record when compared to approved pharmaceuticals. Several comments cited the numbers of serious adverse events associated with approved pharmaceuticals, including deaths, among the U.S. population that are not due to medication errors. For example, various authorities estimate that more than 100,000 deaths per annum are associated with approved pharmaceuticals (Ref. ⁹⁹ and 100). One comment stated that the rate of severe adverse reactions to prescription drugs, without necessarily including misuse, ranks as the fourth to sixth leading cause of death in the United States (Ref. 100). The comment expressed the view that ephedrine alkaloids do not carry a significant or unreasonable risk of harm when compared to the high incidence of serious adverse effects with prescription drugs.

(Response) While we agree that serious adverse events can occur with the use of prescription drugs, that fact does not change our determination that dietary supplements containing ephedrine alkaloids present an unreasonable risk. Prescription medications, although considered safe and effective for their labeled indications, are not free from all risks. However, the benefit of using prescription medications outweighs such risks for particular patients with particular disease conditions, in part because the risk is managed through the physician supervision required for the use of prescription medications. Although dietary supplements need not be free of risks to be lawfully marketed, the risks of using dietary supplements containing ephedrine alkaloids are not outweighed by any benefit. Moreover, it would not be

surprising to see more AERs for prescription drugs than for dietary supplements. Healthcare professionals, who are aware of the drugs prescribed for their patients, are the primary source of drug AERs reported to us directly or through manufacturers. They may not be similarly aware of their patients' use of dietary supplements. In addition, there are no mandatory reporting requirements for dietary supplement manufacturers, unlike for prescription drug manufacturers. Finally, the comments and literature cited pertain to adverse events for all prescription drugs combined. This information has no meaningful bearing on whether dietary supplements containing ephedrine alkaloids present risks.

(Comment 38) One comment contended that dietary supplements containing ephedrine alkaloids should be banned because we have already banned OTC drugs containing ephedrine in combination with caffeine. Numerous other comments stated that our November 18, 1983 (48 FR 52513), prohibition of ephedrine alkaloids combined with caffeine and other stimulants (48 FR 52513) was due to such products' potential for abuse and misuse as illicit street drug alternatives and not because of safety issues. One comment stated that our ~~July 1995~~ ^(60 FR 38643, July 31, 1995) proposal to amend the final monograph for OTC bronchodilator drug products to remove the ingredients ephedrine, ephedrine hydrochloride, ephedrine sulfate, and racephedrine hydrochloride and to classify these ingredients as not generally recognized as safe and effective for OTC use (~~60 FR 38643, July 27, 1995~~) was proposed to restrict the OTC availability of ephedrine because of its illicit use as the primary precursor in the synthesis of the controlled substances methamphetamine and methcathinone. The comment stated that the July 1995 proposal does not

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page 26
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cocaine and amphetamines (Refs. 102 and 103 English abstract), Ephedrine alkaloids exhibit physiological effects common to the amphetamines, but differ in the relative intensity of these effects. We agree that amphetamines and cocaine have been shown to have much greater reinforcing effects and higher liability for abuse than products containing ephedrine alkaloids, but also agree that the development of dependence from the use of ephedrine alkaloids has been noted with both pharmaceutical and botanical products (Refs. 104, 105, and 106). The greater possibility of dependence and abuse of amphetamine-containing and cocaine-containing drug products marketed in the United States is recognized by the placement of these substances in Schedule II of the Controlled Substances Act (CSA). Ephedrine-containing drug products are not scheduled under the CSA; however, ephedrine, its salts, optical isomers, and salts of optical isomers are List I chemicals under the CSA (See 21 U.S.C. 802(34)) because they are chemical precursors of methamphetamine (Schedule II) and are used in its illicit manufacture. As List I chemicals, these substances are subject to various Drug Enforcement Administration (DEA) requirements, including recordkeeping, reporting, and sale behind the counter (See 21 CFR 1310.03 through 1310.07). While we are concerned about the potential for abuse, we did not rely on evidence of abuse or dependence to make our determination under section 402(f)(1)(A) of the act.

(Comment 41) Some comments advocated use of ephedra as an alternative to more dangerous street drugs. They postulated that banning dietary supplements containing ephedrine alkaloids would push those products underground or drive consumers to seek out more dangerous drugs for stimulant effects.

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 and 306700). Since 1997, we have issued a series of warning letters to firms for marketing ephedrine alkaloid-containing products as street drug alternatives and warned consumers not to purchase or consume such products. In March 2000, we issued a guidance document stating that street drug alternatives are unapproved and misbranded drugs that are subject to regulatory action, including seizure and injunction (available at <http://www.fda.gov/cder/guidance/3602fnl.pdf>). Our position was that street drug alternatives are drugs, not dietary supplements, was upheld in *United States v. Undetermined Quantities of Articles of Drug (Street Drug Alternatives)*, 145 F. Supp. 2d 692 (D. Md. 2001). That case involved a seizure of numerous street drug alternatives marketed as dietary supplements, including four products containing botanical ephedrine alkaloids. In January 2003, we witnessed the voluntary destruction of \$4 million worth of illegally marketed street drug alternative products containing ephedrine alkaloids. We continue to address the street drug alternatives with appropriate regulatory actions. We have determined that the appropriate regulatory action for dietary supplements containing ephedrine alkaloids—i.e., products marketed for weight loss, athletic performance, energy enhancement, or other nonstreet drug alternative uses—is to issue a final rule finding that these products present an unreasonable risk of illness or injury.

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

A Congressional subcommittee minority report (Ref. 117), posted at http://www.house.gov/reform/min/pdfs/pdf__inves/pdf__dietary__ephedra__metabolife__rep.pdf noted that the call records from Metabolife International⁴ contain nearly 2,000 reports of significant AERs for its products, including 3 deaths, 20 heart attacks, 24 strokes, 40 seizures, 465 episodes of chest pain, and 966 reports of heart rhythm disturbances. In addition to these cardiac and neurological events, psychiatric symptoms were also reported. These reports include 46 reports of hospitalization following use of their products, and 82 additional reports of emergency room care. The report stated that in more than 90 percent of the most serious AERs— stroke, heart attack, seizure, and psychosis—where dosage information is documented in the call record, the consumer had followed the manufacturer’s dosage recommendations. It also stated that among those most significant adverse event reports for which age was noted, 50 percent of the consumers were under 35 and many of the consumers were reported as being in good health with no prior medical problems. Despite the limited information provided in Metabolife International’s call records, we note that these types of adverse events reported are consistent with the scientifically documented effects and potential risks of ephedrine alkaloids in those cases where appropriate information was available to make a medical evaluation of the reported event.

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

and directions for use in the product's labeling or, if the labeling is silent, under ordinary conditions of use.

b. *Reporting issues, including underreporting*

(Comment 50) Although many comments agreed that the adverse events for dietary supplements containing ephedrine alkaloids were underreported, a number of comments disagreed with our estimates in the June 1997 proposal. Some comments believed that adverse events were less underreported than we estimated, while others thought they were more underreported. One manufacturer stated that it does not report the complaints it receives to us but rather keeps them for its own records.

(Response) As discussed in the response to comment 49 of this document, 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 through 1999, indicated more adverse events than we had received for the same years (Ref. 123). In addition, the Office of the Inspector General of HHS 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 (Ref. 20 at p. 9).

In section VIII.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.

containing ephedrine alkaloids is not necessary to our determination that these products present an unreasonable risk.

c. Interpretation of AERs as supporting the existence of public health risks

(Comment 52) Several comments stated that the number of AERs does not raise a public health concern. One comment asserted that AERs with appropriate use of ephedra are rare. Other comments stated that there is no association between the use of dietary supplements containing ephedrine alkaloids and serious adverse events when used with appropriate dosages, including the American Herbal Products Association (AHPA) trade recommendations. One comment noted that some of the AERs appear to be related to high amounts of ephedrine (i.e., in excess of 500 mg/day) and that the relationship of intake to adverse events with the use of lower amounts consumed is unknown.

(Response) We disagree with these comments. Public health concerns were initially raised by the number of AERs following consumption of dietary supplements containing, or suspected to contain, ephedrine alkaloids in comparison to the number of AERs for all other dietary supplements; the type of adverse event (e.g. cardiovascular system and nervous system effects); and the severity of the adverse events associated with the use of these products. The type, severity, and number of adverse events reported to us prompted us to investigate further. In many of these AERs, including those designated as “most significant” in the Congressional minority report (Ref. 117), the dietary supplement products were consumed as directed on the manufacturer’s label. Although we do not endorse any current trade recommendations for the use of dietary supplements containing ephedrine alkaloids, we note that in many of the AERs, the amounts of ephedrine alkaloids consumed were within the

we have received regarding dietary supplements containing ephedrine alkaloids (Refs. 27 and 109).

The 2003 GAO testimony noted that the adverse event reports are important sources of information concerning health risks of dietary supplements containing ephedrine alkaloids because the regulatory framework for dietary supplements is basically one of postmarketing surveillance and does not require premarket approval. The testimony stressed that despite the limited information obtained from the Metabolife International call records, the types of adverse events reviewed were consistent with the known risks of ephedrine alkaloids, including serious adverse events such as five reports of death. Finally, the testimony noted that several years earlier, we had concluded that dietary supplements containing ephedrine alkaloids present a “significant public health hazard” based upon the adverse event reports received and the consistency of those reports with the known pharmacological effects of ephedrine alkaloids.

C. What Are the Known and Reasonably Likely Benefits of Dietary Supplements Containing Ephedrine Alkaloids?

1. Weight Loss

(Comment 54) Numerous comments, including those from manufacturers and industry trade groups, stated that the results of the RAND report and other evidence, including the CANTOX review and the Boozer et al. clinical studies (Refs. 49 and 125), support or establish the safety and efficacy of dietary supplements containing ephedrine alkaloids for weight loss. Several comments stated that RAND concludes that dietary supplements containing ephedrine alkaloids have proven benefits for weight loss purposes. Several comments stated that RAND shows that dietary supplements containing ephedrine

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style guide
p. 96

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 ephedrine alkaloids could, if they did not present an unreasonable risk of illness or injury, be labeled for ordinary weight loss, they are subject to regulation as drugs if promoted for the treatment of obesity (See 65 FR 1000 at 1026 and 1027, January 6, 2000). We agree with the comments stating that obesity should be treated only with drugs that have been approved as safe and effective for that use.

We do not agree with the comments comparing the effectiveness of dietary supplements containing ephedrine alkaloids for weight loss to approved prescription drugs. The drugs mentioned by the comments are approved for the treatment of obesity, which is a use for which dietary supplements cannot be marketed. Furthermore, we are unaware of any data that have made direct comparisons between dietary supplements containing ephedrine alkaloids for weight loss and drugs approved for the treatment of obesity. As discussed above, prescription drugs for the treatment of obesity are no longer approved on the basis of short-term data or for short-term use. Of note, the few prescription drugs that were approved for short-term use to “jump-start” weight loss are all stimulants and are controlled substances, the first group being approved in 1939 (amphetamine) and the last being approved in 1979 (phendimetrazine). The use of the majority of these drugs has fallen out of favor or the drugs have been withdrawn from the U.S. market. Whether the

loss. In the longest controlled study to date on the effect of ephedrine alkaloid containing products on weight loss by Boozer et al. (2002) (Ref. 49), subjects treated with placebo, plus diet and exercise recommendations, lost an average of approximately 6 pounds over a period of 6 months (Ref. 49). Subjects treated with a proprietary blend of herbal ephedra and kola nut (a source of caffeine), plus diet and exercise recommendations, lost an average of approximately 12 pounds during the same time period. As described previously in the response to comment 22 of this document, 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 1 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))^{ic} 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) study (Ref. 49).

(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

of this document). (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., 1 to 2 hours after a single dose) (Refs. 21 and 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/>

D. Do Dietary Supplements Containing Ephedrine Alkaloids Present an Unreasonable Risk?

1. What Does “Unreasonable Risk” Mean?

A threshold issue is the legal standard of “significant or unreasonable risk of illness or injury” (section 402(f)(1)(A) of the act). By its plain language, this standard requires evidence of “significant or unreasonable risk of illness or injury” (emphasis added).” There is no requirement that there be evidence conclusively demonstrating causation of actual harm in specific individuals. In our evaluation of “significant or unreasonable risk,” we can consider any relevant evidence, including scientific data about the toxicological properties of a dietary ingredient or its mechanisms of action; scientific information about the well-known effects of pharmacologically-related compounds, including those regulated as drugs; the results of clinical studies, including observational studies; and adverse event reports that have been subject to sound scientific analysis. The government’s burden of proof for “significant or unreasonable risk” can be met with any science-based evidence of risk, without the need to prove that the substance has actually caused harm in particular cases.

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 could, over time, and on a population-wide basis, result in hundreds or thousands of adverse events. The Government’s burden of proof for “unreasonable risk” is met when a product’s risks outweigh its benefits in light of the claims and directions for use in the product’s labeling or, if the labeling is silent, under ordinary conditions of use.

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 Corp.*, 529 U.S. 120, 121 (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. Rept. 853, 94th Cong., 2d sess. 19 (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. Rept. 94–1341, 94th Cong., 2d sess. 32 (1976)). Indeed, it is difficult to construct an alternative formulation for the phrase “unreasonable risk.”

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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 context is demonstrated by balancing risks and benefits, our interpretation of an ambiguous provision should receive deference so long as it is “permissible” (*Chevron* Step 2). In interpreting ambiguous statutory language, we are guided by the same criteria we evaluated in Step 1 of the *Chevron* analysis, i.e., the statute’s text, structure, history, and purpose (See *Bell Atlantic Telephone Cos. v. FCC*, 131 F.3d 1044, 1049 (D.C. Cir. 1997); *Chevron U.S.A., Inc. v. FERC*, 193 F. Supp. 2d at 68). Our interpretation of the “unreasonable risk” standard for dietary supplements as requiring a comparison of the risks and benefits of use is consistent with the purpose of the act, as amended by DSHEA, to promote public health and safety. This interpretation is also consistent with the legislative history of the medical device classification provisions.

Therefore, our interpretation that “unreasonable risk” implies a weighing of the risks and benefits of use is, at a minimum, a “permissible construction.”

In the absence of explicit standards for the evaluation of “unreasonable risk,” one comment urged us to be guided by precedent from other agencies. The comment highlighted the Consumer Product Safety Act (CPSA), its implementing regulations, and related case law. The comment stated that any assessment of “unreasonable risk” must include a balancing of risks and

bill does not require it. Further, regulatory action may be taken even though there are uncertainties as to the threshold levels of causation.

(H. Rept. 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 be established along the following lines: (1) A benefit-to-risk ratio below the break-even point would mean that the risks outweigh the benefits and this would justify either a decision to (a) ban dietary supplement products containing ephedrine alkaloids or (b) restrict access to a case-by-case-basis, i.e., prescription; (2) a benefit-to-risk ratio in excess of the break-even point would mean that the benefits outweigh the risks and this would justify continued availability, with appropriate warning labels, dosage instructions, etc.; and (3) a benefit-to-risk ratio equal to the break-even point would mean that the risks equaled the benefits and this would justify either (a) continued availability under the present regulatory framework with appropriate labeling or (b) prescription-only access, whereby a medical professional would make the decision as to whether or not the product was appropriate for an individual consumer on a case-by-case basis.

One comment by a medical association stated that, because dietary supplements are classified as foods, and therefore are assumed to be safe, it is imperative that such products have no risks and provide some benefit to consumers. More specifically, the comment stated that dietary supplements

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 in section V.B.3, ^{of this document} we have seen no data that support any benefit relating to eased breathing in healthy people from dietary supplements containing ephedrine alkaloids. Moreover, as also discussed in that section, because healthy people are able to breathe without difficulty, we do not believe there is any respiratory benefit in the absence of a disease state, such as asthma or a respiratory infection. At the same time, however, there are data that establish the risks of these products. We note that claims to treat or mitigate the effects of a disease subject a product to regulation as a drug under the act.

With regard to other claims such as “feel better,” “feel more alert,” and “energized,” effects of this nature may be of modest benefit to the individual (if they occur), but they are temporary and do not improve health. Therefore, such effects would not be sufficient to outweigh the risks of dietary supplements containing ephedrine alkaloids.

by industry are sufficient to protect the public from any risks. A number of comments proposed different labels to be adopted by the entire industry.

In contrast, many comments maintained that warnings are insufficient and recommended a ban of these products. Several comments pointed out that serious adverse events continue to occur even though most dietary supplements containing ephedrine alkaloids already carry warning statements, such as those recommended by industry trade groups. For several years, warning labels have also been mandated in several states by law or regulation. Many comments noted that, in at least 90 percent of the adverse event reports submitted to us, consumers reported taking dietary supplements containing ephedrine alkaloids as directed on the label.

A few other comments asserted that warning labels are ineffective because serious adverse events have occurred after the initial use or after very short-term use of dietary supplements containing ephedrine alkaloids. As pointed out in the June 1997 proposal, about 40 percent of the 600 AERs reported between 1993 and 1996 occurred with the first use or within ¹one week of first use, providing little or no warning to consumers of risk. Many of the adverse events occurred in individuals who had no apparent risk factors, or who were unaware that they were at risk. ✓

Several comments stated that warning labels on ephedrine alkaloid-containing dietary supplements are not sufficient to protect the public health because many people are not aware they have medical conditions or individual sensitivities that put them at greater risk for experiencing serious adverse effects.

(Response) We agree that warning statements cannot adequately protect consumers from the risks associated with dietary supplements containing

context of dietary supplements containing ephedrine alkaloids. Another comment stated that, with respect to those individuals who are unaware that they may have one of the conditions that is contraindicated on the label, some misuse due to ignorance is unavoidable and occurs no matter what regulations are put in place.

(Response) We do not agree that individuals sensitive to ephedrine alkaloids in dietary supplements are comparable to individuals who suffer from food allergies. In the case of food allergies, individuals learn that they are allergic to certain foods (e.g., shellfish and nuts) and, because we require that the presence of the food ingredients be declared on the food label (see 21 CFR 101.4), these individuals can then avoid the problem ingredient by reading the food label. The physical manifestations of the allergic reaction are usually readily recognized by the consumer. In the case of the ephedrine alkaloids, as discussed previously in the responses to comments 22 and 27 of this document, many individuals are not aware that they are sensitive to sympathomimetic agents, such as the ephedrine alkaloids, and may not recognize early signs of risk, such as elevated blood pressure or the adverse cardiovascular and nervous system effects related to the use of ephedrine alkaloids. In most instances, patients with nascent food allergies experience classic allergy symptoms, such as tingling lips, scratchy throat, wheezing, and shortness of breath, that alert them to the development of a particular food allergy, whereas with ephedrine alkaloids, severe, life-threatening reactions, may occur at any time, even with the first exposure. Therefore, an ingredient declaration or a warning label statement cannot assist these consumers in adequately reducing their risk of adverse events.

B. Multiple Restrictions

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conform to our good guidance practices (21 CFR 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 previously, 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 previously in the responses to comments 39 and 67 of this document, 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. *in this document* ✓ *SR*

F. Targeted Enforcement Actions

(Comment 70) Other comments stated that enforcement actions against products containing extremely high levels of ephedrine alkaloids should be sufficient to address the problem.

(Response) We find that individual enforcement actions against products containing high levels of ephedrine alkaloids are inadequate to protect the public health. Data from the scientific literature and AERs indicate that

App. 2); FDA's implementing regulations (21 CFR part 14); and FDA guidance entitled "Policy and Guidance Handbook for FDA Advisory Committees" (1994) (Ref. 138). We also note that the procedures followed during these meetings were no different from the procedures used in conducting the numerous advisory committee meetings we have held on a variety of other issues.

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

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

Second, the Committees included consumer and industry representatives, including two representatives from associations representing the dietary 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 2 hours of public hearing time, which is twice the time required by our regulations (21 CFR 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

1. Introduction

We have examined the economic implications of this final rule as required by Executive Order 12866. Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). Executive Order 12866 classifies a regulatory action as a significant regulatory action if it meets any one of a number of specified conditions, including having an annual effect

million per year. Therefore, we have determined that this final rule does not constitute a significant rule under the Unfunded Mandates Reform Act.

2. Regulatory Options

We discussed the following seven regulatory options in the benefit-cost analysis of the June 1997 proposal: (1) take no action; (2) take no new regulatory action, but generate additional information on which to base a future regulatory action; (3) take the actions in the June 1997 proposal; (4) take the proposed action, but with a higher potency limit; (5) remove dietary supplements that contain ephedrine alkaloids from the market; (6) take the proposed action, but do not require a warning statement; and 7) require a warning statement only (62 FR 30678 at 30705). We later withdrew all elements of the proposed action except the warning statement and prohibition of dietary supplements that combine ephedrine alkaloids with other stimulants (65 FR 17474). In 2003, we issued a March 2003 notice seeking comment on, among other things, a revised warning statement consisting of a short warning on the PDP and a more detailed warning elsewhere in the product labeling. We did not perform any economic evaluation of the revised warning statement at that time. We received additional comments on the revised warning statement. In addition, the comments on the June 1997 proposal suggested some additional options. Considering the options from these sources, we address the following options in this analysis: (1) Take no new regulatory action; (2) remove dietary supplements containing ephedrine alkaloids from the market; (3) require the proposed warning statement, as revised in 2003; (4) require a warning statement, but modify it or require it only on certain products; and (5) generate additional information or take some action other than removing dietary supplements containing ephedrine alkaloids from the

market or requiring warning statements. Executive Order 12866 requires us to analyze regulatory options but recognizes that there are practical limits to the number of options that we can analyze. The options listed above encompass all or most of the significant suggestions raised in the comments.

3. Summary of Conclusions

We have decided to remove dietary supplements containing ephedrine alkaloids from the market, identified as option 2 above. We estimate net effects would be between -\$47 million and \$125 million per year from this option, if consumer behavior does not already incorporate the health risks posed by these products, and between -\$90 million and -\$7 million per year, if consumer behavior already incorporates the health risks. A detailed discussion of all the options is provided in the following paragraphs.

4. Option One—Take No New Regulatory Action

We use this option as the baseline for determining the costs and benefits of the other options. Therefore, we do not associate costs or benefits with this option. Instead, we discuss the costs and benefits of taking no action in the context of the costs and benefits of the other options. As we discuss more fully under the other options, the expected number of adverse events from these products will probably decline, over time, even if we take no regulatory action, for two reasons. First, many firms are moving away from the use of ephedrine alkaloids because of media coverage of adverse events associated with these products, the high cost of liability insurance, and the potential for legal actions by consumers. Second, some State and local governments have either banned the sale of these products or placed various requirements or restrictions on sales of these products.

5. Option Two—Remove Dietary Supplements Containing Ephedrine Alkaloids from the Market

a. *Benefits of removing dietary supplements containing ephedrine alkaloids from the market.* The benefits of this final rule stem from the reduction of risks brought about by removing dietary supplements containing ephedrine alkaloids from the market. We measure the risk reduction, for the purpose of estimating benefits, as the number of illnesses and deaths averted. Because OMB's guidance to Executive Order 12866 calls for quantification of risk reduction, we place special emphasis in this part of the document on those AERs that lend themselves more readily to quantification.

As shown earlier in this document, dietary supplements containing ephedrine alkaloids would be expected to increase heart rate/rhythm and blood pressure. Increasing blood pressure in any population is associated with increased probabilities of heart attack, stroke, and death, which are the serious adverse events most commonly associated with ephedrine alkaloids. The known pharmacological effects of ephedrine alkaloids lead us to conclude that removing these dietary supplements from the market will reduce the incidence of these adverse events. Estimating the likely reduction, however, presents challenges. One method used in similar situations is to combine data on exposure with a dose-response function to generate estimates of adverse events prevented as exposure declines. We cannot use that method here, however, because we do not have sufficient data on exposure to ephedrine alkaloids from dietary supplements, and we do not know the associated dose-response function. Therefore, the best available approach, and the method we apply here, is to use AERs to generate estimates of the number of adverse events associated with dietary supplements containing ephedrine alkaloids.

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

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

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

control study, this evidence is the best available to estimate the benefits of this rule.

We agree that we should reduce the uncertainty associated with the AERs as much as possible and accurately express any remaining uncertainty. Therefore, we have replaced the baseline number of AERs that we used in the analysis of the proposed rule with the number of AERs that RAND identified as sentinel and possibly sentinel events involving herbal ephedra. RAND identified 20 sentinel events over a period of approximately 9 years from 1992 to 2001, which corresponds to an average of about 2 such events per year. RAND also identified 42 possible sentinel events in this time period, which corresponds to an average of about five such events per year.

We have based our revised estimate on the RAND report because it is the most comprehensive review of the information that is currently available on the safety and efficacy of dietary supplements containing ephedrine alkaloids. However, we acknowledge that considerable uncertainty continues to exist with respect to the number of adverse events that have been caused by ephedrine alkaloids. We have attempted to reflect the continuing uncertainty by updating the assumptions we used in the analysis of the proposed rule, as we discuss in the following paragraphs.

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We did not attempt to forecast trends in the number of adverse events in the analysis of the June 1997 proposal, and we have not done so in this analysis. Forecasting trends in the number of adverse events would be difficult, and any such forecasts would be associated with large uncertainty ranges. Although we recognize that some firms may have recently discontinued the use of ephedrine alkaloids in some or all of their products, we have insufficient information to revise the results of the RAND report on that basis.

Assumptions used in analysis of the final rule

First assumption 90 percent to 100 percent of the sentinel events and 50 percent to 100 percent of the possible sentinel events identified in the RAND report were caused by dietary supplements that we suspect contained ephedrine alkaloids

(Comment 74) A number of comments addressed the first assumption. One comment suggested that we should have set the lower bound of the first assumption to zero because it was possible that none of the AERs had been caused by dietary supplements containing ephedrine alkaloids. Some comments provided their own estimates of the number of AERs that had been caused by those supplements.

(Response) We have revised our estimate of the baseline number of AERs using the number of sentinel and possible sentinel cases identified in the RAND report in order to address the concerns that these comments raised about causation and the presence of ephedrine alkaloids with respect to some of the AERs that we used as a basis for our benefit estimates in the analysis of the June 1997 proposed rule. Although RAND stressed that it could not conclude that these events were definitely caused by ephedrine alkaloids and declined to make any probabilistic statements about causality, the definitions that it used for sentinel and possible sentinel events suggest that those AERs have a relatively high probability of having been caused by ephedrine alkaloids. Therefore, we have revised the assumption concerning the proportion of the AERs that were caused by dietary supplements from 80 percent to a range of 90 percent to 100 percent for sentinel events and 50 percent to 100 percent for possible sentinel events.

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← *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 FAC meetings that nearly 25 percent of the AERs that involved their products involved products that did not, in fact, contain ephedrine alkaloids.

(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 overreport 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 overreport than underreport 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 June 1997 proposal 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 1 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 Britain. One comment estimated the reporting rate for serious adverse events at 50 percent. Another comment estimated the same rate at 10 percent. Both

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 (Refs. 32 and 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 nonsentinel events in the analysis, as explained in the following paragraphs.

ii. *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 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.

(Response) In its guidelines on performing economic analysis of federal regulations under Executive Order 12866, OMB noted that the term “statistical life” can lead to some confusion. It pointed out that this term refers to the

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cases where another condition by itself could have caused the adverse event, but for which the known pharmacology of ephedrine made it possible that ephedra or ephedrine may have helped precipitate the event. We have reflected the uncertainty over causality in the first of the three assumptions that we discussed above. We assume that dietary supplements containing ephedrine alkaloids caused 90 percent to 100 percent of sentinel events and 50 percent to 100 percent of possible sentinel events.

iii. *Serious versus minor adverse events*

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(Comment 79) Some comments suggested that some AERs that we used in the analysis of the June 1997 proposal involved events that we should not have classified as adverse events. These comments argued that these events involved expected side effects of ephedrine alkaloids that are both minor and transient.

(Response) We discussed adverse events that we classified as “less serious” in the analysis of the proposed rule (62 FR 30678 at 30708). However, we indicated that the value of eliminating those adverse events contributed very little to total estimated benefits. RAND did not include these types of more minor adverse events in its sentinel and possible sentinel event cases. Although it did find evidence that products that contained both ephedrine alkaloids and caffeine increased the risk of certain minor adverse events, it noted that it was unable to distinguish the effects of the ephedrine alkaloids and the caffeine. Based on these considerations, we have not attempted to address adverse events beyond those that RAND identified as sentinel and possible sentinel events.

iv. *Risks of substitutes and weight regain*

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*

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(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 removing dietary supplements containing ephedrine alkaloids from the market. Therefore, we discuss these comments under this option.

TABLE 1.—ANNUAL NUMBER OF SENTINEL AND POSSIBLE SENTINEL EVENTS PREVENTED UNDER OPTION TWO (REMOVING DIETARY SUPPLEMENTS CONTAINING EPHEDRINE ALKALOIDS FROM THE MARKET), WITH QALY AND MEDICAL COST PER CASE—Continued

Type	Annual Number Prevented	QALY Loss Per Case	Medical Costs per Case
Psychiatric	0.9 to 1.3	minimal	\$6,927

Note. All dollar values in this document represent 2003 prices.

TABLE 2.—ANNUAL BENEFITS OF OPTION TWO (REMOVING DIETARY SUPPLEMENT CONTAINING EPHEDRINE ALKALOIDS FROM THE MARKET) BASED ON ALTERNATIVE ASSUMPTIONS OF REPORTING RATES AND VALUES OF PREVENTING ADVERSE EVENTS, ROUNDED TO \$ MILLIONS

Value of Avoiding Fatal Cases and QALY Losses	Adverse Event Reporting Rates (in millions)		
	10 percent	50 percent	100 percent
\$ per fatal case = \$5 million \$ per QALY = \$100,000	\$43 to \$73	\$9 to \$15	\$4 to \$7
\$ per fatal case = \$6.5 million \$ per QALY = \$100,000	\$53 to \$91	\$11 to \$18	\$5 to \$9
\$ per fatal case = \$5 million \$ per QALY = \$300,000	\$56 to \$93	\$11 to \$19	\$6 to \$9
\$ per fatal case = \$6.5 million \$ per QALY = \$300,000	\$66 to \$112	\$13 to \$22	\$7 to \$11
\$ per fatal case = \$6.5 million \$ per QALY = \$500,000	\$80 to \$132	\$16 to \$26	\$8 to \$13

c. *Costs of removing dietary supplements containing ephedrine alkaloids from the market.* In the analysis of the proposed rule, we identified the costs that would be generated by removing dietary supplements containing ephedrine alkaloids from the market as the one-time cost of reformulating and re-labeling products that currently contain ephedrine alkaloids, plus the utility loss for those consumers who would need to switch from their preferred option (consuming these products) to their next most preferred option (consuming an alternative product or taking some other type of action) (62 FR 30678 at 30709). In that analysis we did not estimate utility losses for consumers. A number of comments stressed this cost but did not provide estimates of it. Nevertheless, we have revised the analysis by attempting to quantify this cost.

Theoretically, we could measure the utility loss for consumers by looking at the difference between their willingness to pay for products containing ephedrine alkaloids and their willingness to pay for alternative supplements or other substitute products or activities. However, we do not have sufficient information to implement this approach, and may never have a direct measure of the utility loss in this market. Instead, we attempt to measure indirectly the utility loss for consumers of these products. We assume that the premium that these consumers are willing to pay to consume dietary supplements

comparable to any other week. Therefore, we assumed that 2 million consumers use these supplements per day. We then multiplied this number of consumers by the average daily cost of these supplements, which we estimated from a sample of 30 dietary supplements containing ephedrine-alkaloids that we found on the Internet. Based on the recommended intake levels appearing on the labels of these products, the corresponding estimated total sales per year is \$559 million to \$806 million. The costs in the first year after publication of the rule would be slightly different from the cost in every subsequent year because the effective date is 60 days after the publication date of the final rule. Therefore, the utility losses in the first year will be 5/6 (or 83 percent) of the losses of every subsequent year. To simplify the discussion, we use the benefits for every year after the first year in all summary discussions.

Earlier, we assumed that the consumer utility loss from switching from an ephedra-based product to the next closest substitute would be from 1 percent to 10 percent of the sales price at the current level of consumption. Under this assumption and our estimate of total sales, the consumer utility loss associated with removing dietary supplements containing ephedrine alkaloids from the market would be \$6 million to \$81 million per year. The loss of consumer utility would probably decline over time as consumers find more substitute products and as producers develop new, more acceptable substitute products. Eventually, consumer substitutions and product development could drive this cost to zero. We have insufficient information to estimate the rate at which this cost would decline over time.

In the analysis of the June 1997 proposal, we estimated re-labeling costs of \$3 million to \$60 million and product reformulation costs of \$0 million



to \$25 million, for a total cost for these two activities of \$3 million to \$85 million (62 FR 30709). We did not receive any comments on these estimates.

We have, however, revised the analysis to incorporate a new model for estimating reformulation costs that we developed after publication of the proposed rule (Ref. 151). According to that model, reformulation costs with a 12-month reformulation period would be \$7 million to \$78 million. In deriving that figure, we assume that reformulating dietary supplements would not be as complicated as reformulating most other types of food and cosmetics.

In particular, we assume that reformulating dietary supplements would include the following cost generating activities: Idea generation, product research,

analytic testing, packaging development, plant trials, startup, and lost

inventory. We assume that reformulating dietary supplements would not

include the following types of cost generating activities: Process development, coordinating activities, consumer tests, shelf life studies, any type of safety

studies, and market tests. If all of these other steps were involved, then

estimated reformulation costs for a 12-month reformulation period would be

\$22 million to \$142 million. We assume that 6 months is the most likely time

period for reformulation if dietary supplements containing ephedrine alkaloids

are removed from the market. Although the effective date of this rule is 60

days after the publication date, we do not expect that many firms will try to

condense the reformulation process into a 60-day period. Some firms may have

already done some of the preliminary work for reformulation. Other firms

might need to withdraw their product from the market in the period between

the effective date and the date at which they complete their reformulation. The

FDA reformulation cost model does not address costs for a reformulation time

of 6 months, so we extrapolated the costs based on the proportionate change

in cost that would result from halving the reformulation time from 24 months to 12 months. Under that extrapolation, we estimate that reformulation costs for a 6-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 of this document. We compare the benefits and costs of this option in table 4 of this document. 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) *Rounded to \$ millions*

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) *Rounded to \$ millions*

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 \$125
Net Effect (if consumer behavior already incorporates health risks)	-\$90 to -\$7

d. *Distributional issues and impact on industry.* In the analysis of the June 1997 proposal, we estimated that removing dietary supplements containing ephedrine alkaloids from the market would reduce the sales of dietary supplements containing ephedrine alkaloids by between \$200 million and

6. Option Three—Require the 2003 Proposed Warning Statement

a. *Benefits of requiring the 2003 proposed warning statement comparison to removing dietary supplements^{FFI} containing ephedrine alkaloids from the market.* In the analysis of the June 1997 proposal, we noted that estimating the benefit of limiting our regulatory action to requiring the 1997 proposed warning statement involved a potentially controversial value judgment about how one evaluates risks that consumers voluntarily accept in the presence of adequate warning statements (62 FR 30678 at 30711). Our analysis of a mandatory warning statement is further complicated by the fact that the labels of most dietary supplements containing ephedrine alkaloids already bear warning statements.

(Comment 82) One perspective that we discussed in the analysis of the¹ *June 1997* proposed rule² was that adverse events that occur despite the presence of adequate warning statements are not social costs but are instead private costs that reflect informed decisions about the private benefits and costs of using these products. A number of comments agreed with this perspective. One comment argued that consumers have a responsibility to read and follow warnings and instructions for use on products that they consume. Some comments suggested that we should expect consumers to read and follow warning statements, and we should not hold manufacturers liable if consumers fail to do so. One comment argued that we have adopted that viewpoint in other cases involving products that can produce severe adverse effects. Some comments from consumers argued that we should take no regulatory action other than requiring a warning statement because that approach would allow consumers to decide whether or not to assume the risks associated with these products. One comment pointed out that a recent report on the safety of

consideration that suggests that consumers fail to incorporate, at least in part, the probability of adverse events into their market behavior is that some consumers do not know they have the underlying conditions discussed in warning statements.

ii. Comparison to existing warning statements. In economic terms, the benefit of changing a warning statement is the value that consumers place on the change in the information available on product labels. If we had information on how consumers value different warning statements, then we would not need to consider the impact of changing the warning statements on adverse events. Without that information, we must infer the value from the adverse health effects that changing the warning statement would eliminate. This value represents the minimum value of changing the warning statements: Consumers who change their behavior in response to the change in warning statements would presumably be willing to pay the amount that they saved in health costs and lost utility because of that change in warning statements, but some consumers might value the information even though they do not change their behavior. Because the information value for consumers who do not change their behavior is likely to be small, the value of the eliminated adverse events is probably a close approximation to the value of changing the warning statements. Therefore, we have based our analysis on estimating the impact on adverse events of changing the warning statements from the existing voluntary industry warning statements to the proposed mandatory warning statement.

iii. Effectiveness of Warning Statements in Eliminating Adverse Events. In the analysis of the June 1997 proposal, we estimated that the warning statement that we proposed in 1997 would reduce the estimated number of annual

all firms 6 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 of this document, 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

c. *Costs of requiring the 2003 proposed warning statement*

1. *Label Costs*

(Comment 86) Some comments said that the proposed PDP or nonPDP 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, or about 6.6 square inches. The comment argued that the proposed warning statements cannot fit on a label of this size. One comment argued that the proposed warning statement would take up so much space on the label that firms would be able to provide very little other information on the label. One comment argued that there is not enough room on package labels for multiple

one of these ways might require some firms to purchase new packaging machinery, which would be an additional cost beyond the cost of the label changes that we discussed in the analysis of the ^{June 1997} proposed rule. We have insufficient information to estimate the number of products that might need to take these steps. Based on our review of existing product labels, we estimate that the number of such products is probably very small. ✓

We have reestimated labeling costs because we have new information on the number of dietary supplements containing ephedrine alkaloids and we have updated the labeling cost model that we used to estimate labeling costs in the analysis of the June 1997 proposed rule. The cost of changing labels varies with the amount of time that we give firms to change the labels. We previously proposed setting the effective date for this option to be 180 days after the publication of the final rule. According to the revised label cost model, the one-time cost of adding or revising a PDP and a nonPDP warning statement to the labels of all dietary supplements under a 6-month compliance period would be approximately \$140 million to \$319 million. The labeling cost model does not differentiate dietary supplements that contain ephedrine alkaloids from other dietary supplements. However, a database of dietary supplements compiled by Research Triangle Institute (RTI) under contract to FDA listed a total of 3,000 dietary supplement products in 1999, and 49 of those products, or about 2 percent, listed ephedrine or one of the following sources of ephedrine alkaloids in their 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. 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 20 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 20 years at 7 percent gives an annual cost of \$0 million to \$1 million.

d. 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.

(Comment 88) Some comments recommended that we revise the proposed effective date for the warning statement that we proposed in 1997 and revised in 2003. One comment suggested that we set the effective date to 12 months after publication of the final rule, rather than the proposed 180 days after publication of the final rule, to give industry more time to comply with the

benefits over a number of years according to the proportion of products sold during that time that did not bear warning statements. The period over which benefits would be reduced could be quite large because firms might produce as much product as possible prior to the effective date to avoid having to meet the labeling requirements. The comments did not provide information on this issue, and we are unable to estimate this reduction in benefits.

We compare costs of different effective dates for the proposed labeling option in table 7 of this document. We only consider first year net benefits because changing the effective date from 180 days to 365 days only affects benefits in the first year. After the first year, annual benefits would be the same for either effective date. 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. We do not have information suggesting that any of these options would lead to greater net benefits than the proposed enforcement period of 180 days.

TABLE 7.—COMPARISON OF EFFECTIVE DATE OPTIONS FOR OPTION THREE (REQUIRE THE PROPOSED WARNING STATEMENT),
ROUNDED TO \$ MILLIONS

Effective Date	Annualized Cost (mil- lions)	First Year Benefits (mil- lions)	First Year Net Benefits (millions)
180 days	\$0 to \$1	\$0 to \$10	-\$1 to \$10
365 days	\$0	\$0	\$0
180 days at manufacturing site	\$0 plus additional enforcement costs	NA	NA

e. *Conclusions on the Benefits and Costs of 2003 Proposed Warning Statement.* We estimate costs to include the one-time cost of changing the labels of dietary supplements containing ephedrine alkaloids to be \$3 million to \$6 million, which rounds to approximately \$0 million per year (i.e. less than \$500,000 per year) when annualized over 20 years at 3 percent and approximately \$0 million to \$1 million per year when annualized over 20 years

at 7 percent. We are unable to quantify potential recurring countervailing health costs. We estimate the recurring annual benefit to be \$0 to \$20 million, depending on the reporting rate for adverse events, and the method used to value those events. Therefore, we estimate the annual net benefit of this option to be -\$1 million to \$20 million. In the long run, this option would probably generate net benefits, for two reasons: First, the benefits recur annually and any non-zero level of benefits will eventually surpass the one-time labeling cost. Second, as we discussed above, the recurring countervailing health costs are unlikely to exceed the recurring health benefits.

7. Option Four—Require the Proposed Warning Statement, But Modify it or Require it Only on Certain Products.

a. *Require Warning Only for Certain Products.* We discussed a number of comments under Option Two that claimed that certain dietary supplements containing ephedrine alkaloids do not pose any health risks. That discussion is also relevant in the context of exempting certain products from the proposed warning statement. The summary of those comments and our response is the same as under Option Two in section VIII.A.5 of this document. For example, one comment suggested that warning statements are unnecessary for herbal products that firms distribute to “healthcare professionals,” including members of the American Herbalists Guild. We do not have sufficient information to estimate the impact of exempting products based on patterns of distribution or other product characteristics.

b. *Placement and format of warning statement.*

(Comment 89) Some comments addressed the placement of the proposed warning statement on product packages. Some comments suggested that we allow firms to use inserts, stickers, or “peel away” labels. One comment said

eliminating the box graphic would have little effect on costs but would reduce distributional effects and probably also reduce benefits. Requiring a colored box graphic instead of a black and white box graphic would increase costs and possibly increase distributional effects and benefits. Revising the content of the warning statements would have little effect on costs but might increase or decrease distributional effects and benefits, depending on the revision. We have insufficient information to quantify these possible impacts, so we are unable to provide a summary estimate of the costs and benefits of this option.

8. Option Five—Generate additional information or take some action other than removing dietary supplements containing ephedrine alkaloids from the market or requiring warning statements

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(Comment 97) One comment argued that we have no controlled epidemiological studies that support an association between ephedrine alkaloids and stroke, seizure, or myocardial infarction. Other comments noted that RAND said in its report that it was unable to establish that ephedrine alkaloids caused adverse events and that RAND recommended that someone perform a controlled clinical study to address the issue. Another comment noted that Haller and Benowitz (2000) said that their approach did not establish that ephedrine alkaloids caused adverse events and suggested that someone do a large scale case control study to quantitatively determine the risks associated with ephedrine alkaloids (Ref. 34). One comment noted that the NIH National Advisory Council for Complementary and Alternative Medicine Working Group on *Ephedra* suggested that someone perform a multi-site prospective case-control study to assess the risks associated with taking ephedra. This comment suggested that such a study would require 4 to 8 years to complete and cost \$2 million to \$4 million per year. Another comment

is strictly voluntary. The fact that some manufacturers continue to produce dietary supplements containing ephedrine alkaloids despite ongoing and well-publicized concerns about the safety of such products suggests that voluntary guidance documents are unlikely to have a significant effect.

9.B. Benefit-Cost Analysis: Summary

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Removing dietary supplements containing ephedrine alkaloids from the market (i.e. taking this final action) will generate estimated benefits of between \$43 million and \$132 million per year. We used the following assumptions to calculate this range of benefits: A 10 percent reporting rate for adverse events, no potentially countervailing health effects from the use of substitute products and other weight loss alternatives, no countervailing health effects from potentially foregone weight loss, and the fact that consumers do not already understand and incorporate the risks posed by these products in their consumption decisions. Including the impact of substitute products and activities could reduce the rule's health benefit considerably, possibly to \$0 per year, although that is unlikely. These countervailing effects may occur because this rule will not affect the underlying demand for products having functional characteristics similar to ephedrine alkaloids, and it is likely that products having similar functional characteristics may contain similar types of ingredients that may pose similar types of health risks. The range of benefits includes alternative assumptions about the value of a statistical life (\$5 million and \$6.5 million) and the value of a statistical life year (\$0.1 million, \$0.3 million, and \$0.5 million). We also considered a reporting rate of 50 percent, which leads to estimated annual benefits of \$9 million to \$26 million, and 100 percent, which leads to estimated annual benefits of \$4 million to \$13

million. More precise estimates of the health benefits would depend on choosing a particular combination of assumptions.

Removing these products from the market will generate one-time product reformulation costs of \$10 million to \$100 million, which amounts to a yearly cost of \$1 million to \$7 million when annualized over 20 years at an interest rate of 3 percent, and \$1 million to \$9 million at an interest rate of seven percent. These costs could be partly offset by reductions in fees associated with legal actions involving these products. In addition to the social costs, removing dietary supplements containing ephedrine alkaloids from the market could also generate distributional effects under which some firms manufacturing or distributing dietary supplements containing ephedrine alkaloids may experience reduced profits, while firms manufacturing or distributing other dietary supplements or other weight loss alternatives may experience increased profits. In addition, removing dietary supplements containing ephedrine alkaloids from the market would also generate costs in the form of lost consumer utility or satisfaction because of the removal of a product from the market. We estimated lost utility to be \$6 million to \$81 million per year.

Based on these estimates, the potential economic effects of this rule range from a net annual social cost of \$90 million per year, if the rule's net health benefits are zero because of countervailing health effects or because consumers 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.

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

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

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

Option	Annual Cost	Annual Benefit	Net
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 information or take some action other than removal or warning statements	unknown	unknown	unknown

B. Small Entity Analysis

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

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

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

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adulterated. As a result, State laws establishing label requirements or other requirements that contemplate the continued marketing of these products conflict with this final rule and, consequently, are preempted.

Section 4(c) of Executive Order 13132 instructs us to restrict any federal preemption of State law to the “minimum level necessary to achieve the objectives of the statute pursuant to which the regulations are promulgated.” This action meets the preceding requirement because it only applies to state laws that contemplate the continued marketing of this class of products.

Section 4(d) of Executive Order 13132 states that when an agency foresees the possibility of a conflict between State law and federally protected interests within the agency’s area of regulatory responsibility, the agency “shall consult, to the extent practicable, with appropriate State and local officials in an effort to avoid such a conflict.” Section 4(e) of Executive Order 13132 adds that, when an agency proposes to act through adjudication or rulemaking to preempt State law, the agency “shall provide all affected State and local officials notice and an opportunity for appropriate participation in the proceedings.”

In the present rulemaking, consultation with and notice to State officials under section 4(d) and (e) of Executive Order 13132 did not occur before we published the June 1997 proposal. Such consultation and notice was not possible because we published the proposed rule in the **Federal Register** of June 4, 1997, and Executive Order 13132 was not signed until August 4, 1999. OMB’s guidance for implementing Executive Order 13132 states that, when a final rule may have been issued as a proposed rule before August 4, 1999, such that the intergovernmental consultation process had not occurred as called for by Executive Order 13132, the agency’s certification “should so state” (see Memorandum for Heads of Executive Departments and Agencies,

c Ref 161

and Independent Regulatory Agencies, dated October 28, 1999). Thus, we certify that the intergovernmental consultation process described in section 4(d) of Executive Order 13132 did not occur for the proposed rule, but we also believe that State and local governments had sufficient notice and an opportunity to participate in this rulemaking process. We note that the proposed rule was subject to a previous Executive Order, Executive Order 12612, which was also entitled, "Federalism," and had a similar consultation and notification obligation for federal agencies. When we issued the proposed rule, we notified the States, and State and local health departments, among others, submitted comments to the proposal (65 FR 17474, April 3, 2000) (stating that State and local health departments and government agencies had commented on the proposed rule)). Furthermore, a subsequent notice, published on March 5, 2003, expressly asked whether we should determine that dietary supplements containing ephedrine alkaloids present a "significant or unreasonable risk of illness or injury" under section 402(f)(1)(A) of the act (68 FR at 10417, 10419, and 10420). Although the March 2003 notice did not contain a separate Federalism analysis, we believe that States were aware of the March 2003 notice because at least five State or local governments or legislators submitted comments in response to the March 2003 notice, and most of these comments urged us to ban the sale of such products.

XII. References

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

Part 119 259 per Aloma Morris at OFF SR

List of Subjects in 21 CFR ~~SUBCHAPTER B—FOOD FOR HUMAN~~

S. May with complete per. S. L. May

~~CONSUMPTION~~ Dietary ingredients, Dietary supplements, ephedrine alkaloids, significant or unreasonable risks. food SO

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 112 is added as follows:

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PART 112—DIETARY SUPPLEMENTS THAT PRESENT A SIGNIFICANT OR UNREASONABLE RISK

Subpart A General Provisions [Reserved] Subpart B New Dietary Ingredients [Reserved] Subpart C Restricted Dietary Ingredients [Reserved] Authority: 21 U.S.C. 321, 342, 343, 371.

§ 112.1 Dietary Supplements Containing Ephedrine Alkaloids.

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

per DPH 2-34