DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 119

[Docket No. 1995N–0304]

RIN 0910–AA59

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

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

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

DATES: This rule is effective on April 12, 2004.

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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.

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.

Ephedrine alkaloids are members of a large family of pharmacological compounds called sympathomimetics. Sympathomimetics mimic the effects of epinephrine and norepinephrine, which occur naturally in the human body. Multiple studies demonstrate that dietary supplements containing ephedrine alkaloids, like other sympathomimetics, raise blood pressure and increase heart rate. These products expose users to several risks, including the consequences of increased blood pressure (*e.g.*, serious adverse events such as stroke, heart attack, and death) and increased morbidity and mortality from worsened heart failure and pro-arrhythmic effects. Based on the best available scientific data and the known pharmacology of ephedrine alkaloids and similar compounds, we conclude that dietary supplements containing ephedrine alkaloids pose short-term and long-term risks. This is clearest in long-term use, where sustained increased blood pressure in any population will increase the risk of stroke, heart attack, and death, but there is also evidence of risk from shorter-term use in patients with heart failure or underlying coronary artery disease.

The data do not indicate that these products provide a health benefit sufficient to outweigh these risks. The best clinical evidence for a benefit is for weight loss, but even there the evidence supports only a modest short-term weight loss, insufficient to positively affect cardiovascular risk factors or health conditions associated with being overweight or obese. Even if long-term weight loss could be achieved with the use of dietary supplements containing ephedrine alkaloids, we believe that the risks posed by these products when used continuously in the long term generally could not be adequately mitigated except through physician supervision. Other possible benefits, such as enhanced athletic performance, enhanced energy, or a feeling of alertness, lack scientific support and/or provide only temporary benefits that we consider trivial compared to the risks of these products, which may include long-term or permanent consequences like heart attack, stroke, and death. Therefore, we have determined that the risks of dietary supplements containing ephedrine alkaloids, when used for their labeled indications or under ordinary conditions of use, outweigh the benefits of these products. We do not believe these risks can be adequately mitigated through other regulatory measures available to FDA for dietary supplements, such as warnings in labeling.

As with other sympathomimetics, we believe that the risks posed by dietary supplements containing ephedrine alkaloids, when used continuously over the long term, generally cannot be adequately mitigated except through physician supervision. Similar to over-the-counter (OTC) single ingredient ephedrine and pseudoephedrine products, we expect that dietary supplements containing ephedrine alkaloids could be marketed without physician supervision for a very temporary, episodic use that provides a benefit that outweighs the known and reasonably likely risks of these products. However, we are currently unaware of any such use, and our experience with ephedrine alkaloid-containing OTC drug products suggests that such benefits will be demonstrable only for disease uses.

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

The ephedrine alkaloids, including, among others, ephedrine, pseudoephedrine, norephedrine, methylephedrine, norpseudoephedrine, methylpseudoephedrine, are chemical stimulants that occur naturally in some botanicals (Refs. 1 through 5), but can be synthetically derived. The ingredient sources of the ephedrine alkaloids in dietary supplements include raw botanicals (i.e., plants) and extracts from botanicals. Ma huang, *Ephedra*, Chinese *Ephedra*, and epitonin are several names used for botanical ingredients, primarily from *Ephedra sinica* Stapf, *Ephedra equisetina* Bunge, *Ephedra intermedia* var. tibetica Stapf and *Ephedra distachya* L. (the *Ephedras*), that are sources of ephedrine alkaloids (Refs. 1, 6, and 7). Other plant sources that contain ephedrine alkaloids include *Sida cordifolia* L. and *Pinellia ternata* (Thunb.) Makino (Refs. 8 and 9). Common names that have been used for the various plants that contain ephedrine alkaloids include sea grape, yellow horse, joint fir, popotillo, and country mallow. The names desert herb, squaw tea, Brigham tea, and Mormon tea refer to North American species of *Ephedra* that do not contain ephedrine alkaloids but have been misused to identify ephedrine alkaloid containing ingredients. Although the proportions of the various ephedrine alkaloids in botanical species vary from one species to another, in most species used commercially, ephedrine is typically the predominant alkaloid in the raw material (Ref. 10).

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

C. What Regulatory Actions Have We Taken Regarding Dietary Supplements Containing Ephedrine Alkaloids?

In the **Federal Register** of June 4, 1997 (62 FR 30678) (June 1997 proposal), we published a proposed rule on dietary supplements containing ephedrine alkaloids. In this document, we proposed to make a finding, with the force and effect of law, that a dietary supplement is adulterated if it contains 8 milligrams (mg) or more of ephedrine alkaloids per serving, or if its labeling suggests or recommends conditions of use that would result in an 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 June 1997 proposal would also have required that the label of dietary supplements containing ephedrine alkaloids state that the product should not be used for more than 7 days. We also proposed to prohibit the use of ephedrine alkaloids in dietary supplements with other ingredients that have a known stimulant effect that may interact with ephedrine alkaloids, and to prohibit labeling claims, such as weight loss or body building, that require long-term intake to achieve the purported effect. In addition, the June 1997 proposal would have required a statement accompanying claims that encourage short-term excessive intake to enhance a purported effect, such as an increase in energy, that taking more than the recommended serving may result in serious adverse health effects. We also proposed to require that the labels of all dietary supplements containing ephedrine alkaloids bear a statement warning consumers not to use the product if they are taking certain drugs;

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

advising them to contact a health care professional before use if they have certain diseases or health conditions; and warning them to stop use and call a health care professional if they develop certain signs or symptoms. We proposed these actions in response to reports of serious illnesses and injuries, including a number of deaths, associated with the use of dietary supplements containing ephedrine alkaloids and our investigations and assessment of these illnesses and injuries. These actions were also supported by many of the recommendations made during the October 1995 meeting of an ad hoc Working Group of the FDA Advisory Committee (Working Group) and the August 1996 meeting of the Food Advisory Committee (FAC) and the Working Group concerning the potential public health problems associated with the use of dietary supplements containing ephedrine alkaloids and what action FDA should take to address the serious health concerns associated with their use (Refs. 14 and 15).

The comment period for the June 4, 1997, proposed rule ended on August 18, 1997. In a document published in the **Federal Register** of August 20, 1997 (62 FR 44247), we announced our intent to reopen the comment period after we corrected a number of inadvertent omissions in the administrative record. Subsequently on September 18, 1997 (62 FR 48968), we reopened the comment period until December 2, 1997.

During this second comment period, the Commission on Dietary Supplement Labels (the Commission) released its final report on November 24, 1997. The Commission, an independent agency established by section 12 of the Dietary Supplement Health and Education Act of 1994 (DSHEA) (Public Law 103–417), was charged with conducting a study on, and providing recommendations for, the regulation of label claims and statements for dietary supplements. The Commission's members included several scientists from academia and industry. In its report, the Commission divided its conclusions into three categories: findings, guidance, and recommendations. The Commission Report defined ''findings'' as conclusions reached by the Commission based on information and data it received during its deliberations. The Commission defined ''guidance'' that was directed to FDA as advice that we should consider as we developed or implemented activities related to the availability of dietary supplements in the marketplace. The Commission defined ''recommendations'' as suggested changes to FDA regulations or the development of new regulations governing dietary supplements.

One guidance statement in the Commission Report pertains to the safety of dietary supplements containing ephedrine alkaloids. In the report, the Commission urges FDA to use its authority under DSHEA to take swift enforcement action to address potential safety issues such as those posed recently by products containing ephedrine alkaloids. While it is expected that a responsible industry will avoid marketing unsafe products and that the industry will react promptly to remove products shown to be associated with significant or serious adverse events, in the final analysis there must be a strong and reliable enforcement system to back up the safety provisions of DSHEA. Failure by FDA to act when strong enforcement is needed undermines public confidence in the ability of not only the Federal Government but also the dietary supplement industry to ensure safety and avoid harm to the public (Ref. 16 at p. VII of Executive Summary).

In a notice published in the **Federal Register** on April 29, 1998 (63 FR 23633), we announced our views on the recommendations and guidance of the Commission, as presented in the Commission's report. In this notice, we stated that we take seriously our public health protection mission and are committed to removing unsafe dietary supplements from the market (63 FR 23633 at 23634). The direction taken in the current rulemaking on dietary 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 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 June 1997 proposal 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 phenylpropanolomine and hemorrhagic stroke (Ref. 19).

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

In the **Federal Register** of March 5, 2003 (68 FR 10417), we published a notice making available new information about dietary supplements containing ephedrine alkaloids and requesting public comment on the new information and on regulation of these products (68 FR 10417, March 5, 2003) (March 2003 notice). We specifically sought comments on whether, in light of current information, we should determine that dietary supplements containing ephedrine alkaloids are adulterated because they present a significant or unreasonable risk of illness or injury under the conditions of use recommended or suggested in labeling or under ordinary conditions of use if the labeling is silent. The notice also sought comment on a revised version of the warning statement first proposed on June 4, 1997. The revised warning statement had two components, a short warning that would be required to appear on the principal display panel (PDP) and a longer warning that could appear elsewhere in labeling. The proposed PDP warning stated that strokes, heart attacks, seizures, and death have been reported after consumption of dietary supplements containing ephedrine alkaloids and that the risks of adverse events increase with strenuous exercise and with use of other stimulants, including caffeine. The longer proposed warning included more detailed information about risks associated with the use of the product and recommended that consumers avoid using the product and/or consult a doctor under certain circumstances.

In the March 2003 notice, we asked for public comment on all additional evidence developed since the publication of the June 1997 proposal. One such study was a report by the Southern California Evidenced Based Practice Center (the RAND report, RAND, or RAND Corp.), commissioned by the National Institutes of Health (NIH) (Refs. 21 and 22). RAND reviewed recent evidence on the risks and benefits of ephedra and ephedrine[2] and found that dietary supplements containing ephedrine alkaloids are associated with higher risks of mild to moderate side effects such as heart palpitations, psychiatric effects, and upper gastrointestinal effects, and symptoms of autonomic hyperactivity such as tremor and insomnia, especially when they are taken with other stimulants. The RAND report identified 21 ''sentinel events'' among the adverse event reports it reviewed, including stroke, heart attack, and death.[3] RAND also found limited evidence of an effect of ephedra on short-term weight loss. Furthermore, RAND found limited evidence that synthetic ephedrine and caffeine in combination have a short-term enhancement effect on athletic performance in certain physical activities. RAND concluded that the scientific 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 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 despite the limited information contained in most of the call records, 14,684 call records contained reports of at least one adverse event among consumers of Metabolife 356. The GAO testimony identified 92 serious events that included heart attacks, strokes, seizures, and deaths and emphasized that these findings were similar to other reviews of the call records, including those done by Metabolife International and its consultants. The GAO testimony noted that, in those call records where age was documented, many of the serious adverse events occurred in relatively young consumers, with more than one-third being under the age of 30. Furthermore, for those call records in which quantity of use and/or frequency and duration of use were noted, most of the serious adverse events occurred among Metabolife 356 users who used the product within the recommended guidelines, i.e., they did not take more of the product nor consume it for a longer period of time than the product label recommended.

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

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

D. Petitions Received Relating to Dietary Supplement Containing Ephedrine Alkaloids

We received three petitions relating to dietary supplements containing ephedrine alkaloids. The first petition, dated August 27, 1998, was submitted by the American Obesity Association and requested that we issue a final rule on dietary supplements containing ephedrine alkaloids that adopts the regulations in the June 1997 proposal. The second petition, dated October 25, 2000, was filed jointly by the American Herbal Products Association, the Consumer Healthcare Products Association, the National Nutritional Foods Association, and the Utah Natural Products Alliance and requested that we withdraw the remaining portions of our June 1997 proposal and adopt and implement in its place an industry-developed standard for the labeling and marketing of dietary supplements containing ephedrine alkaloids.

The third petition, dated September 5, 2001, was submitted by Public Citizen. This petition requested that we declare dietary supplements containing ephedrine alkaloids adulterated because they present a significant or unreasonable risk of illness or injury under section 402(f) of the act and ban, all production and sales of these products under section 301(a) (21 U.S.C. 331(a)) of the act. The petition also requested that we issue an advisory to stop the use of dietary supplements containing ephedrine alkaloids due to the established risks of injury.

The information cited in support of this petition included:

- Summaries of the updated numbers and types of adverse events reported to us for ephedrine-alkaloid containing dietary supplements compared to the lower incidence of the same types of adverse events reported for all other dietary supplements;
- An FDA preliminary analysis of data collected by and purchased from the American Association of Poison Control Centers (AAPCC) that showed an increase in the number of ephedrine alkaloid-related AERS from 211 in 1997 to 407 in 1999; and
- Adverse events reported to Public Citizen.

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

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

II. Summary of Letters and Comments

We have received more than 48,000 comments in three dockets pertaining to ephedrine alkaloids, Docket Nos. 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 ephedrine alkaloids. More than 13,000 comments opposed a ban of these products and indicated that further restrictions on these products would infringe on personal choice. Thousands of comments requested that FDA not impose stricter regulations on dietary supplements containing ephedrine alkaloids than those imposed on OTC drugs that contain synthetic ephedrine alkaloids. Hundreds of comments requested that we not ban or reclassify ephedra as a prescription drug because, they claimed, such action would result in illegitimate profits for the pharmaceutical companies. Many expressed the view that we should only ban supplements containing excessive amounts of ephedrine alkaloids and those marketed to adolescents and children or to others who may abuse and misuse these products.

Some form letters supported further regulation of these dietary supplement products. Several stated that dietary supplements containing ephedrine alkaloids are dangerous and asked us to ban them. Others requested that we impose more stringent requirements such as mandatory warning labels and maximum dosage levels. Thousands of form letters stated that DSHEA provides us with the necessary authority to protect the public health and that we do not need additional authority. Numerous comments criticized us for failing to exercise the enforcement powers authorized by DSHEA. Numerous form letters requested that ephedrine alkaloids be allowed for professional use by traditional Asian medicine practitioners and dispensed by licensed health care professionals.

We have also received approximately 2,500 individual comments that, although not form letters, did not contain substantive information, analyses, or data. Many of these individual comments raised the same issues as raised in the form letters. Many comments were personal testimonials of how dietary supplements containing ephedrine alkaloids are effective for weight control, improving stamina, or treating medical conditions, and should not be banned or further restricted. Several comments stated that the June 1997 proposal lacked scientific basis and that there are many legitimate studies that support the responsible use of dietary supplements containing ephedrine alkaloids; however, these comments did not submit any additional scientific evidence. Others stated that dietary supplements containing ephedrine alkaloids are safe when used appropriately. Others were personal testimonials of adverse events related to these products that urged a ban or tighter restrictions of these products. Some comments criticized the proposed label warning as too long and ineffective.

Other comments came from members of Congress, with many echoing the issues raised by the form letters. Several congressional representatives commented that Americans are increasingly turning to dietary supplements to improve their health and that Congress passed DSHEA to ensure that these products are regulated

as foods rather than drugs. They cited our own statements that DSHEA gives FDA sufficient authority to remove unsafe dietary supplements from the market. Many urged us to ensure that there was ample opportunity to submit scientific evidence related to dietary supplements containing ephedrine alkaloids. Many urged us to base our decisions on sound science and not rely too heavily on AERs. Some expressed concern about alleged FDA bias against dietary supplements containing ephedrine alkaloids. Others passed on concerns expressed by constituents about adverse health effects from these products. Several comments from members of Congress expressed concern about consumers' ability to read and properly use labels and warnings.

Many of the substantive comments submitted data and other information regarding the use of ephedrine alkaloids. Some comments contained legal analyses of DSHEA and other provisions of the act. Many comments related to provisions of the June 1997 proposal that were withdrawn in 2000 or that have become moot as a result of the action taken in this final rule and, therefore, do not require a response. Examples of moot issues are the proposed prohibition on claims that encourage long-term use and the proposed label statement that the product should not be used for more than 7 days. Other comments addressed issues outside the scope of the rulemaking (*e.g.*, comments about the diversion of ephedrine alkaloids for the illegal manufacture of methamphetamine and methcathinone) and will also not be addressed in this document.

A summary of all relevant comments and our responses to those comments follow. To make it easier to identify comments and our responses, the word ''Comment,'' in parentheses, will appear before the comment summary and the word ''Response,'' in parentheses, will appear before our response. We have also numbered each comment summary to help distinguish between different comment summaries. The number assigned to each comment summary is purely for organizational purposes and does not signify the comments' value or importance or the order in which they were received.

III. Finding of Adulteration

A. What Does the Final Rule Do?

This final rule declares dietary supplements containing ephedrine alkaloids to be adulterated under section 402(f)(1)(A) of the act. We have determined that these products 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 and scientifically established pharmacology of ephedrine alkaloids, the peer-reviewed scientific literature about the effects of ephedrine alkaloids, published case reports of adverse events, and the adverse events reported to us that have occurred in individuals using products containing ephedrine alkaloids, particularly dietary supplements. We have concluded that dietary supplements containing ephedrine alkaloids pose a risk of serious adverse events, including heart attack, stroke, and death, and that these risks are unreasonable in light of any benefits that may result from the use of these products under their labeled conditions of use, or under ordinary conditions of use if the labeling is silent. We are not addressing the issue of whether these products present a ''significant'' risk under section 402(f)(1)(A) of the act.

B. What Products are Covered?

This final rule applies to dietary supplements containing ephedrine alkaloids, including, but not limited to, those from the botanical species *Ephedra sinica* Stapf, *Ephedra equisetina* Bunge, *Ephedra intermedia* var. tibetica Stapf, *Ephedra distachya* L., *Sida cordifolia* L. and *Pinellia ternata* (Thunb.) Makino or their extracts. The ingredient sources of the ephedrine alkaloids include raw botanicals and extracts from botanical sources. Although synthetic ephedrine (in the form of ephedrine hydrochloride) has been found in products labeled as dietary supplements, ephedrine hydrochloride was approved for use as a human drug as early as the late 1940s and, to the best of our knowledge there is no evidence that it was marketed prior to that time as a dietary supplement or food. Furthermore, ephedrine hydrochloride and other synthetic sources of ephedrine cannot be dietary ingredients because they are not constituents or extracts of a botanical, nor do they qualify as any other type of dietary ingredient. For these reasons, products containing synthetic ephedrine cannot be legally marketed as dietary supplements (*See* section 201(ff)(1) and 201(ff)(3)(B) of the act (21 U.S.C. 321(ff)(1) and (ff)(3)(B))). In October 2001, we brought a seizure action against $2.8 million worth of finished drug products containing synthetic ephedrine hydrochloride that were labeled as dietary supplements (*United States* v. *1009 Cases * * * E'ola International AMP II*), No. 2:01CV–820C (D. Utah filed October 22, 2001)). As a result of this seizure, in 2002, the manufacturer signed a consent decree agreeing to the condemnation and destruction of the seized products and prohibiting it from manufacturing or distributing violative ephedrine hydrochloride products. In other actions, we have sent warning letters to multiple firms that were marketing products containing synthetic ephedrine alkaloids as dietary supplements, resulting in the removal of the illegal products from the market.

The final rule does not apply to conventional food products that contain ephedrine alkaloids. Substances intentionally added to a conventional food are generally considered to be food additives under section 201(s) of the act. Ephedrine alkaloids contained in conventional foods would generally be considered unsafe food additives (*see* section 409 of the act (21 U.S.C. 348)). A food that contains an unsafe food additive is adulterated under section 402(a)(2)(C) of the act.

This final rule also does not include OTC or prescription drugs that contain ephedrine alkaloids. The use of ephedrine or pseudoephedrine for the treatment of asthma, colds, allergies, or any other disease is beyond the scope of this final rule. Ephedrine is allowed as an active ingredient in oral OTC bronchodilator drugs for use in the treatment of medically diagnosed mild asthma (§ 341.16 (21 CFR 341.16)), when used within the established dosage limits and when the product is labeled in accordance with the required statements of identity, indications, warnings, and directions for use found in § 341.76. In the near future, we intend to propose revisions to § 341.76 to reflect current scientific information about the risks of ephedrine. Both ephedrine (topical) and pseudoephedrine (oral) are permitted as active ingredients for use as nasal decongestants (§ 341.20), when they are used within the dosage limits established by and labeled in accordance with § 341.80. The topical use of ephedrine will not be further discussed in this rule because it is not relevant to oral consumption of ephedrine in dietary supplements. The use of ephedrine alkaloids in drug products is discussed in more detail in section V.B.3 of this document.

Several *Ephedra* species (including those known as ma huang) have a long history of use in traditional Asian medicine. These products are beyond the scope of this rule because they are

not marketed as dietary supplements. The use of ephedrine alkaloids in traditional Asian medicine is discussed in more detail in section V.B.5 of this document. As we describe there, this rule does not change how these products are regulated under the act.

(Comment 1) One comment stated that we coined the term ''ephedrine alkaloids'' to improperly broaden the scope of the published scientific literature and AERs cited in the June 1997 proposal. The comment pointed out that ephedrine, pseudoephedrine, and phenylpropanolamine (PPA) are all different chemical entities and stated the opinion that only data on ephedrine are relevant to the June 1997 proposal.

(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.B.1 of this document, we recognize that there are some differences between ephedrine and PPA.

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

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

IV. Legal Issues

A. What Is Our Legal Authority Under the Act?

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

> If it is a dietary supplement or contains a dietary ingredient that—
>
> (A) presents a significant or unreasonable risk of illness or injury under—
>
> (i) conditions of use recommended or suggested in labeling, or
>
> (ii) if no conditions of use are suggested or recommended in the labeling, under ordinary conditions of use.

This regulation makes a finding that dietary supplements containing ephedrine alkaloids are adulterated because they present an unreasonable risk within the meaning of section 402(f)(1)(A) of the act. This finding is based on our conclusion that the risks of these products outweigh their benefits. Our legal interpretation of ''unreasonable risk'' is discussed in detail in section V.D.1 of this document. This regulation does not address the meaning of ''significant risk'' or whether dietary supplements containing ephedrine alkaloids present a significant risk under section 402(f)(1(A) of the act.

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

The March 2003 notice asked about the adequacy of FDA's authority to regulate dietary supplements containing ephedrine alkaloids. More specifically, we sought comments on ''what additional legislative authorities, if any, would be necessary or appropriate to enable us to address this issue most effectively'' (68 FR 10417 at 10420).

(Comment 3) Many comments expressed the view that we already have the authority we need to take action against dietary supplements containing ephedrine alkaloids. These comments cited our authority to declare these supplement products to be a significant or unreasonable risk or imminent hazard under section 402(f)(1) of the act or to regulate the products as containing a poisonous or deleterious substance that may render them injurious to health under section 402(a). The comments differed as to whether we had the necessary evidence to utilize these provisions. Several comments opposed any additional authority and criticized us for allegedly not fully implementing the authority we already have.

(Response) We agree that we have the authority to take action against dietary supplements that contain ephedrine alkaloids. All three authorities mentioned by the comments are available to us when circumstances warrant. In this instance, we have chosen to proceed under the adulteration standard in section 402(f)(1)(A) of the act. We believe that we have sufficient evidence to meet this standard.

(Comment 4) In contrast, other comments stated that our legal authority should be strengthened. Several comments expressed the view that DSHEA needs to be amended because it cannot adequately protect public health. One public interest group noted that our delay in acting reflects the difficulty we encounter implementing DSHEA. Several comments offered suggestions for amendments that would strengthen our legal authority, including mandatory reporting of adverse events, certain sales restrictions (*e.g.*, restricting sales to behind the counter only, prohibiting sales to individuals under the age of 18), special labeling requirements for dietary supplements containing ephedrine alkaloids, registration and listing, premarket approval for safety and efficacy (particularly for all new stimulants and steroid substitutes), and repeal of the de novo review provision so that we would receive judicial deference on adulteration issues. A few comments suggested that dietary supplements be regulated as drugs. One comment suggested new legislation to classify dietary supplements according to a risk-based regulatory scheme.

(Response) We must regulate dietary supplements under our existing authority. Accordingly, we are unable to take action regarding suggestions for amendments to DSHEA because any such amendments must result from congressional action rather than rulemaking. Therefore, we are not addressing those suggestions in this rule.

(Comment 5) One comment stated that conventional food safety standards, i.e., the generally recognized as safe (GRAS) standard or the standard for

FDA approval as a food additive, do not apply to dietary ingredients.

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

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

(Response) We disagree with these comments. There are a number of different safety standards for foods (*see*, *e.g.*, section 402(a)(1) and section 402(a)(2)(C) of the act), and whether these standards are higher or lower than the ''significant or unreasonable risk'' standard for dietary supplements in section 402(f)(1)(A) of the act is not relevant to the legal sufficiency of this rule. To the extent that we regulate dietary supplements and conventional foods differently, these differences are justified by the differences in the statutory provisions that apply to these two categories of products. Although some parts of the act apply to both dietary supplements and conventional foods, other provisions apply only to one or the other. Where Congress expressly provided for dietary supplements to be subject to a requirement or standard that does not apply to conventional foods, we may implement that provision without violating the APA. Further, this final rule does not violate the First Amendment. This rule does not restrict speech; rather, it makes a finding of adulteration that results in a prohibition on the distribution and sale of a product that presents unreasonable health risks. Such restrictions on purely commercial, nonexpressive conduct are not subject to First Amendment scrutiny. *See*, *e.g.*, *United States* v. *O'Brien*, 391 U.S. 367, 376 (1968).

(Comment 7) Several comments expressed the view that these products should be regulated as drugs under our existing authority. Some comments stated that we should make these products available only by prescription, arguing that the potential health hazards associated with dietary supplements containing ephedrine alkaloids are too serious for OTC use and that restricting access by requiring a prescription would insert trained medical professionals into a case-by-case decision on the appropriateness of these products to an individual consumer. Further, one comment recommended that if the frequency of adverse events under prescription status does not improve, more restrictive action should be implemented, including the withdrawal of all products containing ephedrine alkaloids from the market.

(Response) We do not agree that all dietary supplements containing ephedrine alkaloids may be regulated as drugs under our existing authority. Products are drugs only if they meet the definition of drug in section 201(g)(1) of the act. Products containing ephedrine alkaloids are regulated as drugs if they are intended to be used in the diagnosis, cure, mitigation, treatment, or prevention of disease (section 201(g)(1)(B) of the act). Without evidence of intended use for such purposes, the product is not a drug under the act. Some dietary supplements containing ephedrine alkaloids are promoted for disease uses, *e.g.*, to treat obesity. In such instances, we can and have taken action against certain dietary supplement products as drugs. Under the act, considerations such as potential risks to health, need for medical supervision, and pharmacology of a product that meets the dietary supplement definition are not by themselves sufficient to subject the product to regulation as a drug.

To the extent that comments suggest that these products could somehow remain dietary supplements but be available only by prescription, we note that we do not have authority to take such action. The act gives us the authority to restrict drugs and devices to prescription use; it does not give us the authority to restrict dietary supplements to prescription use.

(Comment 8) One comment stated that the generally accepted definition of safety for a drug, i.e., a low incidence of adverse reactions or significant side effects under appropriate conditions of use, and a low potential for harm, which might result from abuse situations, is equally applicable to dietary supplements or food.

(Response) We do not agree that the safety standards for drugs apply to dietary supplements or other foods. As explained previously, dietary supplements are not drugs unless they meet the definition of drug in section 201(g)(1) of the act. The same is true for conventional foods. We are basing this final rule on the dietary supplement adulteration standard set forth in section 402(f)(1)(A) of the act. The adulteration standard for dietary supplements set forth in section 402(f)(1)(A) of the act implies a risk-benefit calculus. While we also use a risk-benefit evaluation in the drug evaluation process (*see* § 312.21(c), § 314.50(c)(5)(viii), and § 330.10(a)(4) (21 CFR 312.21(c), 314.50(c)(5)(viii), and 330.10(a)(4))), the act creates different evidentiary standards for dietary supplements and drugs. Therefore, we are not applying the drug safety standard to dietary supplements.

B. Do the Ephedrine Alkaloid-Containing Products Covered by this Rule Fall Within the Definition of Dietary Supplement Under the Act?

A threshold issue is whether the products covered by this rule meet the definition of a dietary supplement under section 201(ff) of the act.

(Comment 9) One comment from a State department of health stated the opinion that dietary supplements containing ephedrine alkaloids present significant risks when they are consumed as a regular part of the diet and do not fall within section 201(ff)(1) of the act. The comment explained that because these products cannot be used on a daily basis without presenting significant risks they cannot be ''intended to supplement the diet'' and are not dietary supplements within the meaning of the act. A related comment expressed the opinion that, for a substance to be a dietary supplement, it must be proven that the human body needs the substance to establish a need for supplementation.

(Response) We agree with these comments in part and disagree in part. We agree that dietary supplements containing ephedrine alkaloids present a risk when consumed as a regular part of the diet; as discussed in section V.B of this document, they present a risk to some users even when consumed occasionally. We do not agree, however, that dietary supplements containing botanical ephedrine alkaloids do not fall within the definition of a dietary supplement in section 201(ff) of the act. Section 201(ff)(1) of the act, added by

DSHEA, provides, in part, that the term ''dietary supplement'' means a product ''intended to supplement the diet'' that bears or contains one or more dietary ingredients. Among the dietary ingredients listed in section 201(ff)(1) of the act are herbs and other botanicals. Therefore, botanical sources of ephedrine alkaloids, such as *Ephedra sinica* Stapf and the other botanicals described in section III.B. of this document, are dietary ingredients. Further, we do not agree that the phrase ''intended to supplement the diet'' authorizes the exclusion of a product from the dietary supplement definition solely on the basis of risk. Given the explicit references to risk in section 402 of the act and the inclusion of botanicals as a category of dietary ingredients in section 201(ff)(1) of the act, it seems clear that Congress intended us to regulate botanical products as dietary supplements (provided that they are not drugs and otherwise meet the dietary supplement definition) and to evaluate their risks under the adulteration provisions in section 402 of the act.

We also do not agree that, under the dietary supplement definition, it must be proven that the human body needs a particular substance to establish a need for supplementation. Under DSHEA, a substance does not necessarily have to be shown to be essential to human nutrition to be marketed as a dietary supplement. Although no provision in the act or legislative history directly addresses this issue, section 201(ff) of the act lists classes of dietary ingredients (*e.g.*, botanicals) that are not essential for growth or to maintain good health (Ref. 28). The fact that Congress classified such substances as dietary ingredients is clear evidence that Congress did not intend to limit dietary ingredients to substances that have been deemed to be essential in human nutrition.

(Comment 10) Several comments, including one from an industry medical consultant, stated that herbal products should not be regulated under DSHEA because they have physiologic effects and significant potential for toxicity. The comment encouraged us to work with industry to establish an appropriate regulatory category for botanicals.

(Response) Under the act (as amended by DSHEA), botanicals can be marketed as dietary supplements provided that they otherwise meet the dietary supplement definition, and are safe and properly labeled. If botanicals meet the drug definition in section 201(g) of the act, they are properly regulated as drugs. In this regard, we published a final rule entitled ''Additional Criteria and Procedures for Classifying Over-the-Counter Drugs as Generally Recognized as Safe and Effective and Not Misbranded'' (67 FR 3060, January 23, 2002). This rule defines the term ''botanical drug substance'' and explains how to submit a time and extent application to request that a botanical drug substance be included in an OTC drug monograph (*see* § 330.14). In addition, we recognize, and are addressing, the current need for guidance for manufacturers seeking to develop botanicals as either OTC or prescription drug products under the applicable statutory and regulatory requirements. (*See* Guidance for Industry: Botanical Drug Products (Draft Guidance) (August 2000) (available at *http://www.fda.gov/cder/guidance/1221dft.pdf*).)

C. Administrative Procedures

(Comment 11) Several comments stated that it is premature to request comments on whether dietary supplements containing ephedrine alkaloids present a significant or unreasonable risk before we define that standard. These comments urged us to undertake a rulemaking, or a guidance document, on this new standard so that it can be applied in the future to all dietary supplements posing health concerns. One comment suggested that defining ''significant or unreasonable risk'' may require new legislation.

(Response) We do not agree that we must define the term ''unreasonable risk'' standard through regulation or guidance before taking action against dietary supplements containing ephedrine alkaloids based upon this standard. An agency may interpret a statutory provision through rulemaking or case-by-case adjudication (*SEC* v. *Chenery*, 332 U.S. 194 (1947)). We conclude, based upon available evidence discussed in section V of this document, that dietary supplements containing ephedrine alkaloids present an unreasonable risk of illness or injury because their risks outweigh their benefits, and that these 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, 842–843 (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. 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.

(Comment 12) Several comments urged us not to act against all dietary supplements containing ephedrine alkaloids because all such products are different and must be considered individually. The comments cited differences in dosages, formulations, labeling, etc., across products and, thus, each product must be analyzed on its own merits. One industry comment argued that we exceeded our statutory authority in trying to regulate all dietary supplements containing ephedrine alkaloids through notice and comment rulemaking.

(Response) We do not agree that we may not regulate the entire category of dietary supplements containing ephedrine alkaloids through rulemaking. We recognize that there are differences between different dietary supplements containing ephedrine alkaloids. However, we conclude, based on available science, that all dietary supplements containing ephedrine alkaloids present an unreasonable risk of illness or injury, regardless of how they are formulated or labeled, because the risks outweigh any benefits that may result from use of the products. Therefore, we may issue a rule finding the entire class of products adulterated.

(Comment 13) A few comments noted that we bear the burden of proof to show

dietary supplements are adulterated under section 402(f)(1) of the act.

(Response) We agree with this comment. Section 402(f)(1) of the act clearly states that in any proceeding under that provision, ''the United States shall bear the burden on each element to show that a dietary supplement is adulterated.'' We have met that burden in this rulemaking.

(Comment 14) Several comments discussed our ability to declare dietary supplements containing ephedrine alkaloids an imminent hazard under section 402(f)(1)(C) of the act.

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

(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 precise proposal which [the agency] may adopt as a final rule''' (*Chemical Manufacturers Association 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 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 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 Co.* 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 *Chem. Mfrs. Ass'n* v. *EPA*, 859 F.2d 977 (D.C. Cir. 1988), the D.C. Circuit distinguished EPA's legal interpretation of unreasonable risk, which received deference under *Chevron U.S.A., Inc.* v. *Natural Resources Defense 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 showing that these products raise blood pressure, published case reports, and AERs, when compared with the evidence regarding the very modest benefits conferred by these supplements, forms a strong factual basis for finding that the known and reasonably likely risks of dietary supplements containing ephedrine alkaloids outweigh the known and reasonably likely benefits of these products. Therefore, dietary supplements containing ephedrine alkaloids present an unreasonable risk of injury or illness under section 402(f)(1)(A) of the act.

(Comment 17) One comment submitted by a trade association noted that, before requesting the Department of Justice to take any civil action against dietary supplements containing ephedrine alkaloids, we must give appropriate notice and opportunity to present oral and written arguments at least 10 days prior to the request.

(Response) We agree with this comment in part and disagree in part. Section 402(f)(2) of the act provides that ''the person against whom such proceeding would be initiated'' must be given notice and the opportunity to present views, orally and in writing, 10 days before we report a violation of section 402(f)(1)(A) of the act (the ''significant or unreasonable risk'' provision) to the Department of Justice for a civil proceeding. By the plain language of this provision, it applies to proceedings against persons, not to proceedings against products. Thus, the requirement applies to injunction actions, which are brought against a corporate or individual person, but not to seizures, which are brought against a product. Therefore, if we were to refer a seizure of dietary supplements containing ephedrine alkaloids to the Department of Justice, the notice requirement would not apply. We further note that the current 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.

V. Scientific Evaluation

A. How Did We Evaluate the Evidence?

To determine whether a dietary supplement presents an unreasonable risk of illness or injury, the agency performs a risk/benefit analysis to ascertain whether the risks of the product outweigh its benefits.

The risks and benefits of a dietary supplement must be evaluated 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 (section 402(f)(1)(A) of the act). Labeling claims for dietary supplements must be substantiated. Unless the manufacturer has substantiation that a labeling claim promoting a dietary supplement for a purported benefit is truthful and non-misleading, the claim misbrands the product (*See* section 403(a)(1) and 403(r)(6) of the act. We note that the standards for substantiating the efficacy of a drug for a labeled indication (i.e., the generally recognized as effective (GRAE) standard for OTC monograph ingredients and the substantial evidence standard for new drugs) do not apply to dietary supplements.

Substantiation of a benefit may not be necessary to lawfully market a dietary supplement if its labeling does not include a claim, and the product poses little or no risk. In weighing risks and benefits to determine whether dietary supplements containing ephedrine alkaloids present an unreasonable risk under section 402(f)(1)(A) of the act, we considered only known and reasonably likely benefits, not speculative benefits. A reasonably likely benefit is one that is supported by a meaningful totality of the evidence, given the current state of scientific knowledge, though the evidence need not necessarily meet the approval standard for a prescription drug.

Although Congress placed the burden on FDA to show ''unreasonable risk,'' once a danger is identified, we do not believe that Congress intended us to delay action until double-blind, placebo-controlled clinical studies could be conducted or that no action be taken if such clinical studies are infeasible or unethical (*see* the response to comment 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. 29, 29a, 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 containing ephedrine alkaloids, it is appropriate to consider the safety of closely related products, such as those with the same active ingredient (*e.g.*, synthetic ephedrine products) or closely related ingredients (such as other sympathomimetics) because we would expect that dietary supplements containing ephedrine alkaloids will exhibit pharmacological effects similar to those other products and, therefore, pose similar risks. It is more difficult to extrapolate conclusions regarding the benefits between an ephedrine drug product and a dietary supplement containing ephedrine alkaloids since the ephedrine drug product is a well defined product with a known dose of ephedrine, while in the latter there is a complex mixture with, possibly, an unknown quantity of ephedrine plus other ephedrine alkaloids, and sometimes other active ingredients, many of which may not be fully characterized. We would need to know how the two products compare with regard to systemic delivery of ephedrine (*e.g.*, the pharmacokinetics profile) to make any judgments about comparable benefits of the two products. If ephedrine pharmacokinetics were the same in a synthetic and plant-derived product and there were no ingredients or components other than ephedrine, one might conclude that the plant-derived and synthetic products would behave similarly. In actual fact, that is not the case because plant derived ephedra products contain other ephedrine alkaloids in addition to ephedrine itself (*e.g.* pseudoephedrine, methylephedrine, and others listed in section I.B of this document). Moreover, if there were other active and inactive ingredients in the plant-derived product, their properties would need to be explored.

In evaluating whether dietary supplements containing ephedrine alkaloids present an unreasonable risk, we looked at the seriousness of the risks and the quality and persuasiveness of the totality of the evidence to support the presence of those risks. We then weighed the risks against the importance of the benefits and the quality and persuasiveness of the totality of the evidence to support the existence of those benefits. We give more weight to benefits that improve health outcomes, especially in the long term, than to benefits that are temporary or rely on subjective measures such as feeling or looking better. For example, sustained, long-term weight loss in an obese or overweight person is a much more important benefit than short-term weight loss because long-term weight loss in these individuals reduces the risk of serious morbidity and mortality (*e.g.*, heart attacks and strokes), while short-term weight loss does not.

In sections V.B, C, and D of this document, we describe the evidence FDA evaluated to reach its determination that dietary supplements containing ephedrine alkaloids present an unreasonable risk of illness or injury.

(Comment 19) Many comments stated that any assessment of unreasonable risk must be based on sound science. Several comments stated that a conclusion about the safety and efficacy of dietary supplements containing ephedrine alkaloids is premature and that additional prospective or retrospective case controlled studies are needed to determine causality. A few comments recommended that FDA, NIH, or other parts of the federal government conduct such research to address unresolved issues of causation. Another trade association urged the government to collaborate with industry to design future controlled studies. Several of these comments cited RAND in support of the need for further research. Several comments noted that the National Center for Complementary and Alternative Medicine/NIH Working Group evaluated the RAND report and suggested a multi-site case-control study to assess the risks associated with these products, although it stated that such a study would take 4 to 8 years and cost $2 to $4 million per year (Ref. 31).

In contrast, several comments asserted that conducting clinical trials of ephedrine alkaloids would be unethical in light of the risks to the human subjects. A professional association stated that FDA regulations that govern drug development and approval would not allow such research, given the absence of information to suggest a benefit that would outweigh the risks. A few comments suggested that any study that could be approved by a human subjects committee would be required to exclude patients at risk and therefore, would not be useful in evaluating risk when the products are taken by the general population without medical supervision. Other comments expressed concern that the additional research recommended by RAND would delay efforts or render it virtually impossible to safeguard public health.

(Response) We recognize the value of properly conducted clinical trials to answer questions regarding the safety and effectiveness of FDA-regulated products. It is not clear, however, that clinical trials to evaluate the adverse effects of ephedrine alkaloids can be conducted. It would not be ethical to study the arrhythmogenic potential of ephedrine alkaloids in patients with coronary artery disease, the adverse effects of ephedrine alkaloids in people with heart failure, or the consequences of raising blood pressure in various populations. Moreover, there is now sufficient evidence, generated through multiple sources, including clinical trials, published literature, and other information, to reach the conclusion that dietary supplements containing ephedrine alkaloids have effects on blood pressure and other pharmacological risks that predict adverse effects in users. After considering the best available information, we conclude that these products present an unreasonable risk 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.

(Response) We do not agree with the comments stating that there is a single accepted method of evaluation to determine when a food ingredient or dietary ingredient in a dietary supplement presents a hazard to the public health. In any evaluation of the risks presented by a substance in a product in the marketplace, the method of evaluating the risk must be applied on a case-by-case basis that is based on the available data concerning the substance being evaluated. We believe that our method of evaluation for ephedrine alkaloids is, however, consistent with that used for other substances. The scientific methodology we used to evaluate the risks associated with the use of dietary supplements containing ephedrine alkaloids consisted of a review and evaluation of the available scientific literature (including literature on pharmacology), clinical studies, published case reports, and other data, including adverse event reports. This is the same type of scientific methodology that is applied in the evaluation of adverse effects associated with other FDA-regulated products (Ref. 32), and includes most of the steps listed in the comments summarized above.

(Comment 21) A number of comments focused on FDA's obligation to ensure that its regulatory assessments are science-based. Two comments raised concern regarding our compliance with a statutory provision popularly known as the Data Quality Act (section 515 of the Consolidated Appropriations Act, 2001, Public Law 106–554, 44 U.S.C.A. 3516 note). One comment stated that we are vulnerable to challenge under the Data Quality Act because there is a disconnect between our proposed actions and the conclusions of the RAND report. Another comment pointed to our related guidance entitled ''Guidelines for Ensuring the Quality of Information Disseminated to the Public'' (*http://www.hhs.gov/infoquality/fda.html#i*). FDA's guidance, which describes how 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 '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.

(Comment 22) Several comments focused on the known pharmacological and toxicological effects of ephedrine/ephedra on the cardiovascular and nervous systems, explaining that ephedra contains vasopressor amines that excite the heart and constrict the blood vessels, which in turn increases heart rate and raises blood pressure. The comments contended that, because of these effects, adverse events such as hypertensive episodes, arrhythmias (abnormal heart rhythms), heart attacks, seizures, and strokes can be anticipated and expected when millions of people are exposed to such products. Various comments maintained that dietary supplements containing ephedrine alkaloids have the same pharmacological and toxicological activity as prescription and OTC ephedrine alkaloid drugs and, thus, present the same risks. One comment emphasized that Chen and Middleton (Ref. 33) warned about ephedrine alkaloid-induced thromboembolism (blood clots that travel in the body) in 1927 and thereafter, reports of toxicity appeared in the medical literature, accompanied by warnings against indiscriminate use by doctors and sale to consumers. These early reports are relevant to current reports of myocardial infarctions (heart attacks) and stroke associated with products containing ephedrine alkaloids.

One comment stated that ephedra presents a danger of prolonged bleeding in those who undergo surgery, and that patients and doctors may not be aware of this potential complication. Another comment cited a review article (Ref. 2) that described myocardial depression occurring with repeated dosing of ephedrine, and cited a reference from a pharmacological textbook documenting ephedrine's tendencies to cause atrial and ventricular arrhythmias. Another comment suggested that we should not ignore the other ingredients commonly found in dietary supplements containing ephedrine alkaloids, such as caffeine, laxatives, and diuretics, because these ingredients can alter electrolyte levels and increase the risk of arrhythmias. One comment, citing a study by Haller *et al.*, contended that the apparent causal role of ephedrine alkaloids in severe adverse effects could be related to the additive stimulant effects of caffeine (Ref. 34). One comment submitted by a manufacturer attributed the good safety record of its product to, among other reasons, the absence of caffeine and other stimulants.

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

Ephedrine alkaloids are members of a large family of sympathomimetic compounds that include dobutamine and amphetamine. Members of this family increase blood pressure and heart rate by binding to alpha- and beta-adrenergic receptors present in many parts of the body, including the heart and blood vessels (Refs. 35, 36, and 37). These compounds are called sympathomimetics because they mimic the effects of epinephrine and norepinephrine, which occur naturally in the human body. In addition to their direct pharmacological effects, many of these compounds also stimulate the release of norepinephrine from nerve endings. The release of norepinephrine further increases the sympathomimetic effects of these compounds, at least transiently. Sympathomimetic effects raise three concerns. First, sympathomimetics can induce cardiac arrhythmias in susceptible people, such as those with underlying coronary artery disease. Second, increased mortality has been observed in patients with congestive heart failure who were treated with sympathomimetic drugs, such as beta-agonists (early studies using such drugs as albuterol led to adverse outcomes) and xamoterol (Ref. 38), as well as phosphodiesterase inhibitors, which potentiate (increase the effect of) the effects of beta-agonists, including milrinone (Ref. 39) and enoximone (Ref. 40). The studies that showed these adverse effects occurred in about 3 months of product use. Third, sympathomimetics can raise blood pressure (Ref. 41).

Based on clinical data, the ephedrine alkaloids present in dietary supplements would be expected to have the same or similar effects as other sympathomimetics on heart rate and blood pressure. Controlled clinical trials using products containing ephedrine alkaloids confirm their typical sympathomimetic effects. Single-dose studies of dietary supplements containing ephedrine alkaloids show that these products cause increases in both heart rate and blood pressure in healthy subjects (Refs. 42, 43, and 44). In one such study of a dietary supplement containing ephedrine alkaloids, the peak increase in blood pressure following a single oral dose of ephedrine alkaloids and caffeine (20 mg/200 mg) was 14 millimeters of mercury (mm Hg) systolic and 6 mm Hg diastolic, occurring about 2 hours after the single dose was taken (Ref. 42).

The findings from these studies are complicated by the presence of caffeine in the dietary supplements used because caffeine is also known to have acute effects on blood pressure and heart rate. However, the effect of caffeine on blood pressure is transient and is lost within 2 weeks of continued 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 blood pressure monitoring device (ABPM); the ABPM method provides more frequent measurements of blood pressure and is, therefore, better able to evaluate blood pressure effects over time. The ephedrine alkaloids and caffeine-treated subjects did not show a difference in the blood pressure measurements taken at the clinic, but did show statistically significant higher average blood pressure measurements over 24 hours at week 4 measured by ABPM (approximately 4 mm Hg for both systolic and diastolic blood pressure) when compared to placebo treated subjects. The ABPM results are shown in a table in the paper. The difference in blood pressure between the two groups represented the sum of small downward changes in the placebo group (compared to baseline) and small upward changes, or no change, in the ephedra group. Boozer *et al.* reported numerous breakdowns of these data (*e.g.*, 6 a.m. to midnight and midnight to 6 a.m.) and characterized the difference between the ephedra and placebo groups as small (about 3 mm Hg) but for the most common ABPM measure, 24-hour value, the difference was 4/4 mm Hg. The observation that this difference (shown in table 2 of the paper) (Ref. 49) reflected a fall in blood

pressure in the placebo group as much as a rise in blood pressure in the ephedra group is not relevant. The only controlled and, therefore, reliable observation is the comparison of the two groups. Small changes from baseline can occur for a wide variety of reasons and are commonly observed in placebo and treated groups. Therefore, the ABPM data are important because they demonstrate that the effect of the ephedrine alkaloids, including dietary supplements containing ephedrine alkaloids, on blood pressure is not transient, but is still evident after 1 month of continued exposure (when measured by ABPM) and, therefore, would be expected to persist long term. The effect reported in the Boozer, *et al.* (2002) study cannot be attributed to the caffeine because the effect of caffeine on blood pressure (discussed previously) is transient, and the acute effect of caffeine to increase blood pressure is lost within 2 weeks of continued use (Refs. 45 and 46). While some effects of sympathomimetics show tachyphylaxis (i.e., decrease in response following repetitive administration of a pharmacologically active substance *http://www.stedmans.com/*) tachyphylaxis usually occurs rapidly. (FDA has verified the Web site address, but FDA is not responsible for any subsequent changes to the nonFDA Web sites after this document publishes in the **Federal Register**.) Therefore, we believe, based upon these data and our experience, that the blood pressure effects of ephedrine alkaloids seen after 4 weeks of continued use will persist.

The Boozer *et al.* (2002) study (Ref. 49) was reviewed at our request by three outside scientific experts, Norman M. Kaplan, M.D. (Ref. 50), Richard L. Atkinson, M.D. (Ref. 51), and Mark Espeland, Ph.D. (Ref. 52). These experts were asked to give their independent, scientific opinion of whether the study provides adequate data to assess safety of ephedrine alkaloids and caffeine for weight loss—considering, among other things, the design and duration of the trial and subject selection—and whether further studies are needed. In general, the experts concluded that the safety of ephedrine alkaloid and caffeine containing products could not be established by this study because the study used a highly selected population (i.e., carefully screened by medical history and medical evaluation to eliminate cardiovascular and other acute or chronic disorders) and had relatively few subjects. One of the experts also concluded that the duration of the study was inadequate to establish safety. In general, the reviewers found that the results raised safety concerns. Dr. Kaplan, one of the reviewers, raised the concern that the size of the change in blood pressure observed with ABPM, when applied to a large population, could translate into a significant increase in the incidence of strokes and heart attacks. Dr. Kaplan's concern reflects the potential consequence of long-term use of ephedra (i.e., the consequence of a population increase in blood pressure). A short-term increase (*e.g.*, 1 to 2 months) would not be expected to have such an effect. Approximately one in four adults has high blood pressure. Of those with high blood pressure, 31 percent are unaware that they have it (Ref. 53). A relative increase in blood pressure in any population, even individuals with ''normal'' blood pressure, will increase the risk of heart attack, stroke, and death in that population (Refs. 29, 29a, and 54).

The extremely high prevalence of diagnosed and undiagnosed hypertension in the U.S. population and the likelihood that blood pressure in obese patients is already elevated make the 4 mm Hg effect shown by the Boozer *et al.* (2002) study (Ref. 49) 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 of dietary supplements containing ephedrine alkaloids. Studies of hypertension treatments suggest that this increase in risk would occur fairly quickly in hypertensive individuals. Anti-hypertensive drugs that lower blood pressure by 4 to 6 mm Hg have been shown to significantly decrease the occurrence of cardiovascular morbidity (stroke, heart attack) and mortality (Refs. 55, 57, and 58). This effect is evident within 6 to 12 months in large outcome studies (Refs. 29 and 30). FDA is concerned about the adverse health effects that can occur with the use of agents that raise blood pressure, such as dietary supplements containing ephedrine alkaloids, for short- or long-term use. Even in the case of a controlled clinical trial of a possible hypertension treatment where subjects are closely monitored, we advise sponsors to limit the length of time subjects can be in a placebo/untreated group to about 8 weeks to minimize their exposure to cardiovascular risks from the absence of treatment.

As noted previously, the pharmacological effects of ephedrine alkaloids also present increased short-term risks of adverse health events in susceptible populations. For example, there is evidence from peer-reviewed scientific literature that a wide range of drugs with sympathomimetic activity, including beta-agonists, phosphodiesterase inhibitors, and dobutamine, have adverse effects (increased mortality due to heart failure and sudden death) in patients studied with congestive heart failure. These effects have been seen in relatively short-term studies (Refs. 59, 60, and 61) Similarly, there are studies that document that people with coronary artery disease are more susceptible to the well-known pro-arrhythmic effects of sympathomimetics (Refs. 62, 63, and 64) The occurrence of such an arrhythmic event is not one that requires prolonged exposure but would represent a risk associated with each use, including the first. Many individuals are unaware that they have coronary artery disease or early heart failure because these conditions may not cause prominent symptoms until later in the course of these conditions. As a result, we are concerned that such individuals will not know that they are at an increased risk for developing significant cardiovascular adverse events from even short-term use of dietary supplements containing ephedrine alkaloids. Overweight and obese individuals are particularly prone to hypertension, coronary artery disease, and/or heart failure, as overweight and obesity are associated with these conditions (Refs. 65 and 66). These conditions may not manifest clinically until later in the course of the condition and, therefore, individuals, including overweight and obese individuals, may be unaware they have these conditions. As a population, the overweight and obese are, thus, at a greater risk even from short-term use of sympathomimetics.

As summarized previously, the comments cited certain literature suggesting the possibility of additional adverse effects of ephedrine alkaloids,

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

(Comment 23) Various comments did not agree that there are risks with products containing ephedrine alkaloids and stated the opinion that cardiovascular side effects associated with products containing ephedrine alkaloids in several blinded studies were not significantly different in control and treatment groups. Several comments maintained that there is no evidence from clinical studies that ephedrine ''supplementation'' increases peak heart rate, peak blood pressure, or the prevalence of cardiac arrhythmias. Another comment contended that ''clinically relevant doses'' of ephedra have no clinically significant effect on pulse or blood pressure, and produce no measurable alterations in myocardial function. A number of comments noted that changes in heart rate and blood pressure are transient and similar to those produced by exercise. Several comments stated that the effects of ephedra combined with caffeine on blood pressure are modest and generally subside over the first few days of use. Other comments stated that, although dietary supplements containing ephedrine alkaloids have a relatively high incidence of subjective and cardiovascular side effects with first use, the side effects diminish with continued use due to tachyphylaxis. Several comments noted that the literature, including the obesity studies we cited in the June 1997 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 (compared with placebo) at the end of 1 month of therapy (Ref. 80a). This difference was observed when blood pressure was measured throughout the day, using ABPM, but not with cuff blood pressure measurements (a less sensitive measure). This difference in results using different measurement methods may have confused some readers and led them to conclude that ephedrine alkaloids do not have a clinically meaningful effect on blood pressure. The fact that an effect on blood pressure (as measured using ABPM, which follows measurements throughout the day) was still present at 1 month strongly indicates that tachyphylaxis to the effects of ephedrine does not occur. As discussed in the response to comment 22 of this document, tachyphylaxis tends to occur rapidly, as with caffeine, whose blood pressure raising effect is lost within 2 weeks. Therefore, FDA does not agree with the comments expressing assurances that adverse effects will disappear with continued use of ephedrine alkaloids because of tachyphylaxis.

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

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

We do not agree that the clinical studies establish that ephedrine does not have adverse pharmacological and clinical effects. The published controlled studies of the use of ephedrine alkaloid products for weight loss cited by these comments cannot establish the safety profile of these products. First, many of the most serious risks, such as strokes or heart attacks (consequences of elevated blood pressure), arrhythmias, or worsened heart failure, are relatively infrequent or are delayed and, therefore, will not be detected in studies using small populations (such as under 100 patients per group) as these studies did. Second, these studies often had other important design limitations, such as lack of adequate controls (including the absence of placebo groups in some studies), and inadequate information about the causes that led to participants dropping out of the trial. In addition, persons with known cardiovascular disease or cardiovascular risks were usually excluded. Thus, these studies were not designed to detect serious adverse effects in susceptible individuals, nor to detect adverse effects that occur infrequently. As discussed in the following paragraphs, these studies were also not adequately designed to assess blood pressure effects. Given these limitations, it is not surprising that these published studies do not report serious adverse events (Refs. 21, 22, 50, 52, and 81).

These trials also would not have been able to detect effects on blood pressure because of other design limitations. For example, when sponsors of drug products seek to detect a drug-induced decrease in blood pressure in patients with hypertension, the trial is specifically designed to perform the following functions: (1) Assess the blood pressure effects at both peak and trough levels of the drug in the blood, and (2) measure blood pressure in a consistent and reproducible manner. This typically requires the enrollment of at least 100 patients to detect a difference from placebo of around 4 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 because of the clinical trial design limitations (Refs. 81a, 81b, and 81c), 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. 29, 29a, and 54), as can ephedrine's sympathomimetic effects in people with coronary artery disease or heart failure, but the kinds of damage seen in humans from these effects would look the same as similar damage that occurs from the underlying disease or from raised blood pressure or arrhythmia due to another cause.

(Comment 24) A number of comments discussed the relevance of PPA to regulatory decisions on dietary supplements containing ephedrine alkaloids. Several comments stated that PPA is a metabolite of ephedrine. Various comments contended that ephedrine and PPA are both partial agonists and that adverse events associated with dietary supplements containing ephedrine alkaloids are of the same type and greater in number than those associated with PPA, which was voluntarily withdrawn from the U.S. market for safety reasons. Other comments maintained that we should not use PPA data to support the hazards of dietary supplements containing ephedrine alkaloids. Several such comments stated that because PPA differs in pharmacological, pharmacokinetic, and pharmacotoxic effects from ephedrine or pseudoephedrine, it is scientifically inappropriate for us to assume that all ephedrine alkaloids are equivalent. Other comments asserted that the various isomers of ephedrine alkaloids have different actions, different favorable and adverse effects, different activation of receptors, and different effects on human tissues. Several comments indicated that norephedrine (an ephedrine alkaloid that makes up one component of PPA) is a metabolite of ephedrine and that interactions of the multiple ephedrine alkaloids in *Ephedra* and other botanicals and their *in vivo* metabolites should be considered in a safety evaluation of these ingredients and products containing them.

A few comments asserted that the Hemorrhagic Stroke Project (HSP) (Ref. 19) was not designed to assess ephedra exposure. These comments maintained that the HSP is limited by significant issues relating to observation bias, selection bias, and confounding. One comment complained that we reopened the ephedra docket requesting comment on the HSP, but we did not place in the docket, or request comment on, the many published and unpublished clinical studies submitted by one trade organization to support PPA's safety. The comment asserted that our review of the pharmacology of ephedrine alkaloids did not include most of the pivotal information on PPA submitted to us by the Consumer Healthcare Products Association (CHPA). Another comment expressed the view that, in our review of safety data related to ephedra, we should avoid relying on safety data concerning other ingredients.

(Response) The substance, l-norephedrine, also known as (-)-norephedrine, refers to the isomeric portion of PPA that occurs naturally in *Ephedra* and as a metabolite of ephedrine in the body. We agree that the l-norephedrine in racemic PPA is a metabolite of ephedrine, and further that ephedrine and its metabolites have potent vasoactive properties, reinforcing the view that dietary supplements containing ephedrine alkaloids have the pharmacological properties described in the response to comment 22 of this document. These properties, in turn, are linked to predictable adverse clinical outcomes both in the general population (*e.g.*, increased blood pressure) and in susceptible populations (*e.g.*, cardiac arrhythmias). Although there are some similarities between PPA and ephedrine, there are also differences. PPA shows tachyphylaxis to rises in blood pressure within approximately 24 hours and usage has been linked to hemorrhagic strokes (bleeding strokes due to a ruptured blood vessel). Ephedrine does not show such tachyphylaxis. In addition, use of ephedrine has been associated with ischemic strokes (a blood clot blocking off an artery causing a lack of oxygen to portions of the brain), but not hemorrhagic strokes. The major alkaloid in most dietary supplements containing ephedrine alkaloids is generally ephedrine, and not norephedrine (Ref. 82).

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

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

(Response) Given that *Ephedra* and other botanicals used as dietary ingredients contain a mixture of ephedrine alkaloids, and given the small database on the supposed selective effects of the isomers, we cannot draw any reassurance from the possibility that one alkaloid has more or less of an effect on the vasculature (or organ systems) than another alkaloid. Further, the reported differences in receptor binding affinity or other *in vitro* tests cannot eliminate concern about the effects of ephedrine alkaloids in humans, because there is clinical evidence that ephedrine alkaloids have important pharmacological effects (*e.g.*, increased blood pressure, heart rate) that persist, particularly in the case of ephedrine, through at least 1 month of use. As noted previously in this document, the

major alkaloid in most dietary supplements containing ephedrine alkaloids is generally ephedrine (Ref. 82). The comments pointing to evidence of differences in the effects of different ephedrine alkaloids do not provide a basis to conclude that dietary supplements containing ephedrine alkaloids do not present an unreasonable risk of illness or injury.

(Comment 26) Some comments argued that the scientific literature indicates that single doses of ephedrine up to 60 mg generally do not increase blood pressure (Ref. 83). Other comments cited a handbook of intravenous drug therapy for nurses that states that ephedrine is of low toxicity. One comment stated that the scientific literature describing the effects of ephedrine in doses of 50 to 150 mg does not support the contention that ephedrine in dosages of 50 to 150 mg per day would represent a health hazard. Many comments stated that reviews of the literature and other data by independent experts reflect the scientific consensus that ephedrine alkaloids at 25 mg per dose are safe. One comment cited a clinical study of 98 elderly patients undergoing hip surgery who received 0.6mg/kg ephedrine by intramuscular injection. One out of 48 patients in the placebo group and two out of 50 in the ephedrine group experienced increased heart rate or increased systolic blood pressure greater than 20 percent from baseline. The comment concluded that the dosages used are greater than the dosages found in any dietary supplement containing ephedrine alkaloids and that the results of the study are consistent with the conclusion that, as also asserted by other comments, no significant injury has been clearly associated with dietary supplements containing ephedrine alkaloids when used as directed.

We received numerous other comments dealing with the issue of ''safe'' doses for ephedrine alkaloids in dietary supplement products. Many expressed the view that low doses of ephedrine alkaloids in dietary supplements do not pose a safety concern and should remain on the market.

(Response) We do not agree that the scientific literature indicates that there is a dose of ephedrine or ephedrine alkaloids that does not present a risk of adverse events. Although dosages vary in dietary supplements containing ephedrine alkaloids, most products are labeled with 20–25 mg ephedrine alkaloids per recommended serving and 100–150 mg ephedrine alkaloids per day. Some of the doses described in the comments as safe (50 to 150 mg ephedrine alkaloids per day) are in the range studied by Boozer *et al.* (90 mg ephedrine alkaloids per day) (Ref. 49) and, thus, could cause an increase in blood pressure, a significant health concern (*see* previous discussion). We also do not agree that some lower dose of ephedrine has been demonstrated not to increase blood pressure and heart rate. The relationship between a given dose of ephedrine and changes in heart rate and blood pressure has been poorly characterized, although it is clear that ephedrine is capable of increasing both. As discussed in the response to comment 23 of this document, the published studies that have found no effects on blood pressure and/or heart rate have had methodological deficiencies that limited their ability to detect such changes. With respect to the clinical study of 98 elderly patients, the failure to find serious adverse events is understandable, as the study was designed to demonstrate that intramuscular ephedrine was effective to prevent hypotension related to spinal anesthesia. The concern that led to the study was adverse events related to an expected decrease in blood pressure resulting from the anesthesia. As would be expected based on the pharmacology of ephedrine, the study showed that ephedrine is effective in maintaining blood pressure in patients receiving spinal anesthesia.

We do not agree with comments that suggest that low doses of ephedrine alkaloids in dietary supplements do not present an unreasonable risk and should remain on the market. Because this issue was raised in comments responding to the June 1997 proposal, we commissioned a scientific review that was placed in the 2000 docket (Refs. 84 and 85). This review concluded that a ''safe dose'' of ephedrine alkaloids cannot be identified. The review determined that even ''a dose of 1.5 mg every 4 hours (a daily dose of 9 mg) would produce cardiovascular effects that may be dangerous alone, or in association with risk factors* * *'' (Ref. 84 at p. 6). We also note that in the 1996 FAC meeting, several committee members stated that, based on the available data, no safe level of ephedrine alkaloids could be identified for use in dietary supplements (Ref. 86). Consequently, they recommended removing dietary supplements containing ephedrine alkaloids from the market (Ref. 87). Although the CANTOX Health Sciences International (CANTOX) review attempted to establish a level of ephedrine alkaloids at which there were no adverse effects, we do not consider the information submitted sufficient to establish a ''safe'' dose (*see* discussion of CANTOX in the response to comment 32 of this document).

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

(Response) We agree with the comments that expressed concern about the effects of ephedrine alkaloids on susceptible populations and have previously discussed long-term and short-term risks to susceptible populations in the response to comment 22 of this document. There is every reason to expect that certain populations will be more susceptible to the adverse effects of ephedrine alkaloids and that many such people will not be aware of their greater susceptibility. As noted previously, people with coronary artery disease, early congestive heart failure, and high blood pressure, all of which are more

common in obese individuals, are often unaware of these risk factors. Thus, the recommendations contained in the comments regarding the suitability of dietary supplements containing ephedrine alkaloids for certain populations and the need to consult a physician if the consumer has certain preexisting conditions are ineffective to mitigate the risk that dietary supplements containing ephedrine alkaloids pose to these susceptible populations.

(Comment 28) Several comments stated that warning labels on dietary supplements containing ephedrine alkaloids are not sufficient to protect the public health because many individuals are not aware they have medical conditions or individual sensitivities that put them at greater risk for experiencing serious adverse effects.

The comments stated that warnings are ineffective for individuals who are not aware that they have disease conditions such as high blood pressure or other cardiovascular diseases, hyperactive thyroid function, undiagnosed cerebrovascular abnormalities, or a propensity for cardiac arrhythmia, seizure or certain psychiatric disorders. The same comments maintained that even small amounts of ephedrine alkaloids can be potentially dangerous to 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 sections V.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 ephedrine alkaloids would either be contraindicated or pose a potential safety concern.

In contrast, a physician who used dietary supplements containing ephedrine alkaloids in his practice stated that he was as comfortable with people using dietary supplements containing ephedrine alkaloids on their own, as he was with people using an OTC drug product on their own.

(Response) We generally believe that the risks posed by dietary supplements containing ephedrine alkaloids when used continuously, particularly in obese patients who may already have underlying illnesses that can be aggravated by these products (such as hypertension), cannot be adequately mitigated without physician supervision. Sustained high blood pressure has significant consequences, including increased risk of stroke, heart attack, and death. As noted previously, even short-term use of dietary supplements containing ephedrine alkaloids poses certain risks, such as arrhythmias in patients with coronary artery disease. While we allow ephedrine and pseudoephedrine in OTC drugs for temporary, episodic uses, such as the temporary relief of symptoms (shortness of breath, tightness of chest, and wheezing) of certain diseases (*e.g.*, colds, allergies, previously diagnosed bronchial asthma, colds, allergies) individuals who use dietary supplements containing ephedrine alkaloids for reasons other than to improve their health (*e.g.*, to lose weight for improved appearance) obtain no health benefits and at the same time are at risk for the types of adverse events that can occur with both short and long-term use of ephedrine alkaloids. As discussed more thoroughly in section V.C.1 of this document, use for relatively short term weight loss would give, at best, a weight loss of a few pounds, which would not be sufficient to result in any health benefit. However, use for weight 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. 49).

(Comment 31) Many comments contended that we failed to consider the differences among ephedrine alkaloids from the raw botanical; extracts from the raw botanical that contain unaltered proportions of alkaloids and other substances; concentrated and/or otherwise manipulated ephedra extracts such that naturally occurring proportions and/or quantities of ephedrine alkaloids are changed; and synthetic or pure isolated ephedrine (extracted as a single entity from the plant). Because these products have chemical differences and differences in

potency, toxicity, pharmacokinetics, and pharmacological and physiological effects, the comments maintained they should be considered separately in scientific, medical, and regulatory contexts.

Other comments, citing a study by White *et al.*, stated that other natural constituents, including other alkaloids and ephedradines in the raw botanical, modify or attenuate the physiological and pharmacological effects of the ephedrine contained in dietary supplements (Ref. 43). Numerous comments maintained that raw *Ephedra* and/or *Ephedra* extracts are safer than ephedrine that is synthetic or that has been isolated and that serious adverse events associated with the appropriate use of ephedra have been rare. Several comments asserted that the ephedradines have hypotensive effects and are found in ephedra roots, rather than the aerial portions of the plant. One comment maintained that ephedradines are thought to occur in small amounts in *Ephedra* stems. One comment stated that ephedra extract is safer than pharmaceutical ephedrine based on the fact that the LD_{50} is higher for the botanical extract (5.4g/kg) when compared to the LD_{50} for pharmaceutical ephedrine (64.9 mg/kg) (''LD_{50}'' refers to the amount of a material that causes death in 50 percent of test animals).

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

Other comments maintained that there is no difference between blood levels of ephedrine from botanical sources and ephedrine contained in OTC drugs. Comments from a State Board of Pharmacy stated that ephedrine from botanical sources is neither safer than, nor different from, pharmaceutical ephedrine. One comment objected to our including clinical studies using pharmaceutical ephedrine in our evaluation. A number of comments suggested that naturally occurring ephedrine is more potent than its synthetic counterpart. A few comments stated that the presence of varying amounts, proportions and chemical configurations of ephedrine alkaloids in crude *Ephedra* and prepared *Ephedra* extracts, as well as the presence of unknown compounds, leads to uncertainty in dose, purity, and composition and a greater risk for adverse effects. Comments noted that this variability is not an issue for synthetic or pure isolated ephedrine alkaloids.

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

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

Regarding the ephedradines, we are not aware of any evidence in the scientific literature, nor were any data provided in the comments, that indicate that these compounds are present in *Ephedra*, in other botanical sources of ephedrine alkaloids, or in extracts from these botanicals. The ephedradines are known constituents of the roots of the species *Ephedra sinica* Stapf (Ref. 90). In traditional Asian medicine, the roots and rhizome of the plant are referred to as ''ma huang gen,'' while the aerial parts of the plant are referred to as ''ma huang'' (Ref. 3). The ephedradines are not ephedrine alkaloids. Nor are they present in the aerial parts of the plant that are used in dietary supplements. The scientific evidence, thus, does not support the opinion that the other ephedradrines in the raw botanical act to modify or attenuate the physiological and pharmacological effects of the ephedrine alkaloids contained in these products.

We do not agree, therefore, that current evidence establishes that ephedrine alkaloids from botanical sources, including botanical extracts, are different from, or are any safer than, pharmaceutical ephedrine alkaloids. With regard to the comment asserting that ephedra extract is safer than pharmaceutical ephedrine because the LD_{50} is higher for the botanical extract than the LD_{50} for pharmaceutical ephedrine, we note that scientific views on this point differ. Another scientific reference suggests that a mixture of ephedrine alkaloids from a botanical extract may be more toxic, based on LD_{50} calculations, than an equal amount of pharmaceutical ephedrine (Ref. 91). While there is not enough scientific evidence to draw a conclusion, we acknowledge the possibility that other components in the concentrated extracts (*e.g.*, tannins derived from the botanical) may affect the toxicity of botanical preparations of ephedrine alkaloids (Refs. 89 and 92).

2. Other Safety Data

(Comment 32) Many comments cited multiple data and information sources as support for the safety of dietary supplements containing ephedrine alkaloids. These cited sources have been submitted to the docket and include the CANTOX review, RAND Report, the Ad Hoc Committee on the Safety of Ma Huang report and the Ad Hoc Committee on the Safety of Dietary Supplements, *Ephedra* Education Council Expert Panel Report, and a 6-month clinical trial by Boozer *et al.* (2002) (Refs. 21, 49, 93, 94, 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 for ephedrine alkaloids used in dietary supplements because it was flawed. Its flaws include use of an inappropriate risk assessment model and deviation from the criteria and procedures established by IOM, including relying on abstracts and unpublished articles, using an unsuitable definition of ''Tolerable Upper Intake Level'' (UL), and using an overly narrow definition of ''adverse effect.''

The IOM model referenced by CANTOX is the Food and Nutrition Board's report entitled ''Dietary Reference Intakes: A Risk Assessment Model For Establishing Upper Intake Levels For Nutrients.'' The introduction to this report states that dietary reference intakes are being established for ''nutrients and food components'' which include nutrients, dietary antioxidants, micronutrients including electrolytes and fluid, macronutrients, ''and other food components not traditionally classified as ''nutrients,'' but purported to play a beneficial role in human diets'' (Ref. 28 at pp. 1 and 2). The IOM report defined dietary reference intakes, in part, as ''reference values that are quantitative estimates of nutrient intakes to be used for planning and assessing diets for healthy people. They include both recommended intakes and [tolerable upper intake levels] as reference values'' (Ref. 28 at p. 2). The report defined ''Tolerable Upper Intake Level'' (UL) as ''the highest level of daily nutrient intake that is likely to pose no risk of adverse health effects to almost all individuals in the general population. As intake increases above the UL, the risk of adverse effects increases'' (Ref. 28 at p. 3). The rationale for establishing such a risk assessment model is that nutrients are an essential part of the diet and deficiency states result when they are absent from the diet or are available in too low of a concentration.

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

Even if the IOM dietary reference intakes model were an appropriate risk assessment model for dietary supplements containing ephedrine alkaloids, we note that CANTOX deviated from the IOM's criteria and procedures in several important ways. For instance, the IOM report used studies published in peer-reviewed journals as the principal sources of data for its evaluations. In contrast, while CANTOX did use some publications, it also relied on abstracts and unpublished studies. For example, CANTOX cited the study by Boozer, *et al.* as the pivotal study demonstrating the safety of dietary supplements containing ephedrine alkaloids and the establishment of the NOAEL. However, the Boozer (Ref. 96) study was only available in abstract form at the time of the CANTOX review. Abstracts are not subject to the same rigorous peer review that full manuscripts go through. Further, abstracts do not contain sufficient information to enable a reader fully to evaluate a study's methodology or independently to interpret or verify a study's results. As a result, abstracts should not be given the same weight as the full reports of studies themselves. In the case of the Boozer study, the abstract did not provide details on the exclusion or inclusion criteria for the study, so a reader could not determine how the subjects were selected or how they were monitored during the study. The CANTOX authors also did not acknowledge the significance of the blood pressure findings in the Boozer *et al.* As we have discussed extensively in section V.B.1 of this document, this study by Boozer *et al.* (Ref. 49) clearly demonstrates a higher blood pressure in ephedra plus caffeine treated subjects (compared to placebo), which translates into serious long-term risks in the general population and serious short-term risks in susceptible populations. Furthermore, as stated by outside scientific experts who reviewed this study, the Boozer *et al.* (2002) study cannot establish the safety of dietary supplements containing botanical ephedrine alkaloids and caffeine because the study used a highly selected population, had relatively few subjects and was carried out for too short a period of time. Rather, the Boozer study raises questions about the safety of these products.

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

We also note a number of other deviations from the IOM's application of its risk assessment model (Ref. 28). Compared to the definition in the IOM report, CANTOX expanded the definition of the UL and narrowed the population to which it applies. As noted earlier, the IOM report defined the UL, in part, as ''the highest level of daily nutrient intake that is likely to pose no risk of adverse health effects to almost all individuals in the general population.'' The IOM report stated that the term ''tolerable'' was chosen ''because it connotes a level of intake that can, with high probability, be tolerated biologically by individuals; it does not imply acceptability of that level in any other sense.'' The IOM report also noted that ''the UL is not intended to be a recommended level of intake'' (Ref. 28 at pp. 3, 4, and 5). The IOM report also stated that ''the critical endpoint used to establish a UL is the adverse biological effect exhibiting the lowest NOAEL (for example, the most sensitive indicator of a nutrient or food toxicity). The derivation of a UL based on the most sensitive endpoint will ensure protection against all other adverse effects'' (Ref. 28 at p. 18). The IOM report also explained that, ''When possible, the UL is based on a NOAEL, which is the highest intake (or

experimental oral dose) of a nutrient at which no adverse effects have been observed in the individuals studied. This is identified for a specific circumstance in the hazard identification and dose-response assessment steps of the risk assessment'' (Ref. 28 at p. 10).

Although CANTOX defined the UL as ''the maximum level of chronic daily intake of a substance judged unlikely to pose a risk to the most sensitive members of the health population,'' their UL determination was based upon the ''specified conditions of use,'' which includes label warnings that these products not be used by many in the general population (including those under 18 years, pregnant or lactating women, and persons with certain health conditions, including those most sensitive to the effects of these products, *e.g.*, persons with hypertension and coronary artery disease). In contrast, the IOM concept of the UL is the highest level of intake likely to pose no risk of adverse health effects to almost all individuals in the general population. Thus, the CANTOX UL is less protective than the IOM UL because it removes from its risk assessment the members of the population who would be most at risk for adverse effects of dietary supplements containing ephedrine alkaloids.) (Ref. 93 at p. 5).

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 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.

Finally, we discuss the inadequacies of the publications used by CANTOX to assess the safety of ephedrine alkaloids in section V.B.2 of this document. Whatever methods are employed, these deficiencies in the data used in CANTOX's analysis significantly undermine any conclusions reached in the CANTOX report.

(Comment 33) Several comments objected that we did not consider animal studies using ephedrine alkaloids to evaluate the safety of ephedrine alkaloids as dietary ingredients, as several comments noted had been done in the CANTOX review. One comment stated that the results of the National Toxicology Program's long-term rodent studies on ephedrine showed that a lethal dose of ephedrine alkaloids for most animal species, translated into human consumption, was between 200 and 400 25 mg tablets. A related comment referred to toxicity (LD_{50}) studies comparing pharmaceutical ephedrine with ma huang in mice, emphasizing lesser toxicity of ma huang: The LD_{50} for ephedrine alkaloids from ma huang was 5300 mg/kg body weight versus 689 mg/kg for pharmaceutical ephedrine. A related point from this comment was that wild and domestic animals consume *Ephedra* shrubs and there are no reports of adverse effects in these animals. One comment included data from rat, mouse, and dog toxicity studies on a specific ephedrine alkaloid-containing dietary supplement. The results and their interpretation by consultants were offered as demonstrating a very low toxicity for the supplement. One comment stated that no animal study suggests that the ephedrine alkaloids would be harmful at human doses of 25 mg per serving. One comment stated that animal and laboratory testing may be informative on some issues but, in and of itself, cannot answer the human causation question.

(Response) We recognize the value of animal studies in identifying or predicting the toxicological properties of substances for human exposure. In fact, animal studies do identify the sympathomimetic effects of ephedrine that underlie our concern. These would not be expected to lead to harm in healthy laboratory animals because these animals do not have coronary artery disease or other susceptibility to arrhythmias or congestive heart failure. An effect of elevated blood pressure, if large and sustained, might perhaps show effects in very large, long-term animal studies, but there is no reason to think that a modest effect, one that would increase hypertensive risk in humans but still lead to a low overall risk in any individual, would be detectable in animals. The animal data are, therefore, not at all reassuring. The discussion of the consumption of wild *Ephedra* species by wild and domestic animals contributes no relevant safety information, since these animals also lack pertinent human risk factors (coronary artery disease, heart failure, elevated blood pressure). Also, were these animals to have an adverse effect, there would be no way to identify it. However, we believe, as stated previously, that there is sufficient scientific evidence from multiple sources, including clinical trials and the published literature pertaining to use of ephedrine alkaloids in humans, to conclude that dietary supplements containing ephedrine alkaloids pose serious risks of illness or injury.

3. Comparison with Drug Products Containing Ephedrine Alkaloids

(Comment 34) One comment asserted that our proposal to treat dietary supplements more restrictively than OTC drugs containing ephedrine and pseudoephedrine is in violation of the Administrative Procedure Act's prohibition on rulemaking that is arbitrary and capricious. According to the comment, OTC ephedrine and pseudoephedrine products contain higher doses 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 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 record of OTC drugs containing ephedrine alkaloids is evidence of the safety of dietary supplements containing ephedrine alkaloids. Several comments asserted that there is a lack of serious AERs for both traditional Asian herbal products and OTC ephedrine drugs with dosages based on FDA's monograph (less than or equal to 25 mg per serving and less than or equal to 150 mg in a 24-hour period) and that these dosages are, thus, safe.

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

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

As discussed previously, all sympathomimetics may pose risks for adverse events even after a single dose. GRASE status does not mean that an OTC drug product may not cause adverse events. In fact, there have been adverse events reported to FDA concerning ephedrine- and pseudoephedrine-containing OTC drugs. There are also numerous adverse event reports for dietary supplements containing ephedrine alkaloids. The incidence and type of adverse event reports related to dietary supplements containing ephedrine alkaloids are discussed in section V.B.6 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 relieved within 1 hour or become worse (§ 341.76(c)(5)). As discussed in the response to comment 34 of this document, the benefits of ephedrine and pseudoephedrine drug products for disease claims are different from the benefits of dietary supplement products for nondisease claims, so it would be inappropriate to conclude based on OTC drug product information that these dietary supplements do not present an unreasonable risk. No data demonstrate that dietary supplements containing ephedrine alkaloids provide a meaningful health benefit to a particular

population for any specific use and for short periods of time, as is the case for OTC ephedrine or pseudoephedrine drug products. Therefore, we have determined that the risks presented by dietary supplements containing ephedrine alkaloids (including heart attack, stroke, and death) outweigh their benefits, and that these products are adulterated regardless of what warnings are included in their labeling. We note that dietary supplements containing ephedrine alkaloids may also present other, less serious risks listed in the required warnings for OTC drugs containing ephedrine and pseudoephedrine; however, because we are removing these dietary supplement products from the market based on their cardiovascular risks, we are not addressing these other risks in this rule.

With regard to the comments that discussed safety data for OTC ephedrine bronchodilator drugs specifically, we note that the studies used to evaluate ephedrine for the treatment of asthma and those using ephedrine alkaloids for weight loss and other nondisease uses enrolled different populations and used different study designs, endpoints, and monitoring protocols. Therefore, comparisons across patient populations or indications (*e.g.*, asthma treatment versus weight loss) for a risk benefit analysis is not justified. FDA's 1986 final rule finding ephedrine GRASE as a bronchodilator was based on the 1976 recommendation of the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products (the Panel) (*See* 51 FR 35326, October 2, 1986 and 41 FR 38312 at 38370 to 38372, September 9, 1976). The Panel relied on data from studies conducted in 1973 and 1975 (Refs. 97 and 98). These studies were designed to examine the efficacy of terbutaline as a bronchodilator. The patient population enrolled in these studies were not only clinically stable (i.e. normal electrocardiogram, blood pressure, and pulse) but also had no apparent history of adverse events related to treatment with other stimulant bronchodilators used at the time. These studies support the use of ephedrine for patients with asthma who are otherwise clinically stable (i.e. not found by a physician to have high blood pressure or other cardiovascular risk); however, they do not support the safety or efficacy of dietary supplements containing ephedrine alkaloids for weight loss or other nondisease uses.

(Comment 36) Several comments asserted that it is misleading to compare the safety and efficacy of ephedra to OTC drugs because all drugs are toxic to some individuals and all products must be evaluated on the basis of their benefits relative to their risks. These comments expressed the view that dietary supplements containing ephedrine alkaloids have only limited benefit for weight loss over placebo and that this modest weight loss has never been shown to reduce the increased morbidity that is associated with obesity.

(Response) We agree that dietary supplements containing ephedrine alkaloids and OTC drug products must be evaluated based on a comparison of their risks and benefits. It should be noted, however, that the evidentiary standards for evaluating these two categories of products are different. We have done a risk-benefit analysis for dietary supplements containing ephedrine 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 (Refs. 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 proposal (60 FR 38643, July 27, 1995) (July 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 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 discuss the safety of the use of ephedrine and thus does not support our actions.

(Response) We do not agree that our July 1995 proposal did not discuss the safety of OTC bronchodilator drug products containing ephedrine alkaloids (60 FR 38643 at 38644). In any event, comments about the basis and scope of our 1983 prohibition on ephedrine and caffeine combinations in OTC drug products and the 1995 ephedrine drug product proposal are not relevant to this rulemaking because we are not relying on those actions as a basis for the

removal of dietary supplements containing ephedrine alkaloids.

4. Abuse and Misuse

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

(Response) We agree that directions for use, warnings, and other labeling must be considered when making an assessment of significant or unreasonable risk. Section 402(f)(1)(A) of the act provides that whether a dietary ingredient or dietary supplement presents a significant or unreasonable risk must be evaluated ''under conditions of use recommended or suggested in labeling,'' except that ordinary conditions of use may be considered if the labeling is silent on conditions of use. Thus, for purposes of the ''significant or unreasonable risk'' provision, unless no conditions of use are recommended or suggested in labeling, we must consider a dietary supplement's labeled use rather than its actual use. We do not agree, however, that our evaluation of significant or unreasonable risk should be based on the standards specified in AHPA's *Ephedra* Trade Recommendation (Ref. 101). These standards are voluntary recommendations by a trade association and are not universally followed. We must consider all dietary supplements containing ephedrine alkaloids, not just those formulated and labeled in accordance with the *Ephedra* Trade Recommendation. In this instance, we conclude that all dietary supplements containing ephedrine alkaloids present an unreasonable risk, regardless of whether they are formulated and labeled in accordance with the *Ephedra* Trade Recommendation, based on our evaluation of the totality of the evidence and a weighing of the risks and benefits of the products. As discussed in section VI.A of this document, the presence of a warning label or of directions recommending a limit on daily consumption of ephedrine alkaloids does not sufficiently reduce the risks of dietary supplements containing ephedrine alkaloids to allow them to continue to be marketed as currently labeled or under ordinary conditions of use, and the risks of these products outweigh their benefits regardless of labeling.

(Comment 40) Several comments compared the effects of ephedra to other sympathomimetics such as cocaine or amphetamine. Several other comments stated that while ephedrine, PPA, and amphetamine are similar in chemical structure, they differ in physiological effect, and that amphetamines have much stronger reinforcing effects and a much higher liability for abuse than ephedrine. One comment stated that the subjective effects of ephedrine more closely resemble caffeine. Another comment stated that amphetamines do not have direct agonist properties, but promote release of neurotransmitters and inhibit their deactivation and reuptake. One comment from a manufacturer of a dietary supplement containing ephedrine alkaloids stated that its product label warns consumers not to take the product longer than 12 weeks because it can be habit forming and to take it longer runs the danger of ''getting hooked.''

Several comments expressed the opinion that ephedrine alkaloid dependence is similar to amphetamine dependence, as are the psychological effects of abuse such as psychosis, paranoia, and the potential to cause mania in susceptible individuals. Comments from several individuals and the founder of a consumer advocacy Web site included anecdotal reports of individuals who reported dependence or apparent addiction associated with use of ephedrine and dietary supplements containing ephedrine alkaloids. Several other comments cited the German Commission E monograph's instructions to limit the use of ephedra preparations to short-term because of the danger of addiction. (The Commission E was a division of the German Federal Health Agency established in 1978 to evaluate the safety and efficacy of herbal medicines sold in Germany. It produced official monographs for botanicals and botanical formulations sold in German pharmacies.)

(Response) We agree that ephedrine alkaloids and amphetamines share some pharmacological and physiological properties that may be associated with abuse and dependence. Psychostimulant effects that have been reported with sympathomimetic agents include drug tolerance, dependence, or addiction, although these psychostimulant effects are better recognized for cocaine and amphetamines (Refs. 102 and 103 of 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.

(Response) No data were submitted with these comments to support their conclusions. We have no information regarding the extent of use of ephedra, or dietary supplements containing ephedrine alkaloids, as an alternative to more dangerous street drugs, nor do we have any information about whether users of ephedrine alkaloids would be likely to use other substances were ephedra to become unavailable. Regardless, such information would not affect the determination we have made that dietary supplements containing ephedrine alkaloids present an unreasonable risk.

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

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

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

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

5. Traditional Asian Medicine

(Comment 44) Many comments stated that the use of ephedrine alkaloids in dietary supplements is safe based on its traditional use in Asian medicine for thousands of years. Several comments asserted that few or no adverse effects have been recorded with the use of *Ephedra* in traditional Asian medicine. Numerous other comments, including those by traditional Asian medicine practitioners, disagreed with these comments about dietary supplements, highlighting the differences in the products themselves and how they are used from what is used in traditional medicine.

Several comments suggested that the raw *Ephedra* and *Ephedra* extracts used in traditional Asian medicine formulae differ in potency, toxicity, pharmacokinetics, and pharmacological and physiological effects from many dietary supplements containing ephedrine alkaloids and, therefore, that these formulations should be considered distinct in scientific, medical, and regulatory contexts. Comments stated that ''*Ephedra*'' properly refers to dried aerial parts of medicinal plants, or crude extracts thereof, not to isolated alkaloidal constituents. Several comments further distinguished the various products containing *Ephedra* as follows: Herb and extracts of raw herb of medicinal *Ephedra* plants containing naturally occurring alkaloids and other compounds without further manipulation, concentration, or adulteration; *Ephedra* extracts that are concentrated, manipulated, or adulterated such that naturally occurring proportions and/or quantities of ephedrine alkaloids are altered; products containing ephedrine alkaloids combined with other agents such as caffeine, caffeine-containing herbs, salicylate-containing herbs, synephrine, and other substances; and traditional Asian herbal medicinal formulae.

Several comments asserted that traditional Asian medicine *Ephedra* formulae often deliver lower amounts of ephedrine alkaloids compared to other types of ephedrine alkaloid-containing products and that traditional formulae rarely contain more than 15 percent *Ephedra* in the herb mixture. Comments also asserted that *Ephedra* in traditional formulae is usually combined with other botanicals that typically modify *Ephedra*'s inherent stimulant effects. Another comment attributed the relative safety of *Ephedra* to the mixture of ephedrine alkaloid isomers not present in purified or synthetic alkaloids. One comment suggested that the established therapeutic dose range of *Ephedra sinica* in herbal medicine formulae is 60 to 90 mg total alkaloids per day (adults), which falls within the dosage range established for OTC ephedrine/pseudoephedrine-containing drugs (150 mg and 240 mg alkaloids daily, respectively), and the recommendations of the Germany Commission E (maximum daily *Ephedra* alkaloid dose of 300 mg daily). Other comments asserted that infusions or teas of *Ephedra* are effective in relieving respiratory symptoms but have fewer side effects and are safer than formulations containing isolated or synthetic ephedrine alkaloids or prescription drugs. Another comment stated that supplements in a liquid tea form greatly reduce the risk of excess acute consumption by the public.

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

Numerous comments, including those by traditional Asian medicine practitioners, also noted differences in how the products are used. Several comments stated that most traditional Asian uses of *Ephedra* are the same as the indications for OTC ephedrine and pseudoephedrine drugs (*e.g.*, short-term use to improve respiratory function) and that few if any adverse effects have been recorded. Several comments stated that use of *Ephedra* (ma huang) for weight control or for its stimulating effects, for more than a short period of time, in combination with caffeine and other botanical stimulants, and without the supervision of a health care provider, is irresponsible and dangerous. A number of traditional Asian medicine practitioners maintained that many

consumers experienced adverse effects because of this improper use, overdosage, or conflict with their illnesses.

Because of these differences, many practitioners of traditional Asian medicine commented that they support our June 1997 proposal except to the extent that it would restrict their use of *Ephedra* in traditional Asian medicine. Several comments asserted that since most serious adverse effects involve use of ephedrine alkaloids and not whole herb or whole herb extracts of *Ephedra*, any rule must exempt whole herb *Ephedra* or whole herb *Ephedra* extracts that contain no added ephedrine alkaloids. Furthermore, ephedrine alkaloid-free species of *Ephedra* should also be exempted.

Numerous comments asserted that because traditional Asian herbal products are prescribed by appropriate practitioners (licensed, certified, and registered acupuncturists, herbalists, and naturopathic physicians) and because these products are not associated with serious adverse effects, the products do not appear to constitute a public health risk and their use should not be prohibited. Many traditional Asian medicine practitioners stated that *Ephedra* is an essential medicine and requested an exemption from the final rule for use of *Ephedra* by traditional Asian medicine practitioners and acupuncturists. A few comments asserted that *Ephedra* should not be used commercially, but be restricted to professional use, to be dispensed by licensed health care professionals trained in the appropriate use of traditional Asian medicine.

(Response) This final rule does not affect the use of *Ephedra* preparations in traditional Asian medicine, although we considered the comments' views and information on the use of *Ephedra* in traditional Asian medicine in the context of their possible relevance to the risks of dietary supplements containing ephedrine alkaloids. This rule applies only to products regulated as dietary supplements (*See* 62 FR 30678 at 30691). Traditional Asian medicine practitioners do not typically use products marketed as dietary supplements.

With respect to the absence of adverse effects recorded with the use of traditional Asian medicine, as we stated in the June 1997 proposal, we are not aware of any systematic collection of data related to adverse effects occurring in individuals treated with *Ephedra* in traditional Asian medicine. The absence of recorded adverse events with the use of *Ephedra*, therefore, may be related to the lack of a mechanism for reporting. Under these circumstances, there are no data to evaluate. We note that the potential for adverse effects resulting from the traditional Asian use of *Ephedra* is implied in several reference texts that list precautions and contraindications for the use of the botanical *Ephedra* in traditional Asian medicine preparations (Refs. 3, 107, and 108). Moreover, even if we could say that the absence of recorded adverse events with the use of *Ephedra* in traditional Asian medicine was due to its safety for that use rather than due to a lack of mechanism for reporting, the history of use of *Ephedra* in traditional Asian medicine primarily for the treatment or mitigation of respiratory illness cannot provide assurance about the safety of dietary supplements containing ephedrine alkaloids for other uses.

6. Adverse Events

AERs involving drugs include those submitted to us voluntarily by consumers or healthcare professionals and those submitted by manufacturers who are required to report them to us. However, there is no required reporting of AERs to us for dietary supplements, including those containing ephedrine alkaloids. Depending on other information we may have about the event or about the suspect product, AERs can be hard to interpret. AERs may raise concerns about a product, as well as buttress a finding that a particular dietary supplement represents an unreasonable risk based on other types of evidence. Some AERs can be reasonably persuasive on their own. For example, individual cases of adverse events where dechallenge (discontinued use) and rechallenge (restarting use) have been linked to the abatement and recurrence of the events, strongly support the association between exposure to the product and occurrence of the adverse event. FDA, and others, have reviewed and analyzed the AERs in depth to add to the body of evidence and to ensure that all relevant evidence is considered (Refs. 109 through 115). Despite the limitations of such reports, a detailed review of the AERs submitted to us for dietary supplements containing ephedrine alkaloids and comparison of those AERs to scientific data about the pharmacology of these substances establishes that the AERs are consistent with the known and expected pharmacological effects of these products considered (Refs. 109, 115, and 116).

In the preamble to the June 1997 proposal, we stated that there were more than 800 reports of illnesses and injuries associated with the use of dietary supplements containing ephedrine alkaloids. Since that time, we have received more than 2,200 additional AERs submitted directly to us plus approximately 16,000 reports from call records submitted by Metabolife International, one of the largest distributors of dietary supplements containing ephedrine alkaloids. These records have been placed in the record for this rulemaking in redacted form.

A Congressional subcommittee minority report (Ref. 117), posted at *http://www.house.gov/reform/min/pdfs/pdf__inves/pdf__dietary__ephedra__metabolife__rep.pdf* [4] noted that the call records from Metabolife International contain nearly 2,000 reports of significant AERs for its products, including 3 deaths, 20 heart attacks, 24 strokes, 40 seizures, 465 episodes of chest pain, and 966 reports of heart rhythm disturbances. In addition to these cardiac and neurological events, psychiatric symptoms were also reported. These reports include 46 reports of hospitalization following use of their products, and 82 additional reports of emergency room care. The report stated that in more than 90 percent of the most serious AERs— stroke, heart attack, seizure, and psychosis—where dosage information is documented in the call record, the consumer had followed the manufacturer's dosage recommendations. It also stated that among those most significant adverse event reports for which age was noted, 50 percent of the consumers were under 35 and many of the consumers were reported as being in good health with no prior medical problems. Despite the limited information provided in Metabolife International's call records, we note that these types of adverse events reported are consistent with the scientifically documented effects and potential risks of ephedrine alkaloids in those cases where appropriate information was available to make a medical evaluation of the reported event.

(Comment 45) Many comments criticized our system for collecting and evaluating adverse events and our use of AERs. A number of comments criticized the reporting system, stating that many of the received reports were insufficiently documented and lacked critical information necessary for appropriate evaluation. Other comments stated that the reports were anecdotal

[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 that no scientific standards were used in their evaluation.

Several comments stated that our attempt to rely on AERs for attributing adverse events to dietary supplements containing ephedrine alkaloids is in conflict with established scientific principles and FDA policy. The comments cited the criticism of our reliance on AER in the July 1999 GAO Report, our bases for regulation of Yellow No. 5 which included AERs and multiple clinical studies, and the opinion that our AER review system was biased and lacked scientific rigor.

Several comments stated that our methods of data collection might have affected the integrity of the data. The comments explained that we included in the database AERs that had not been verified. Many of these comments also stated that adverse events were frequently reported by family members and FDA officials rather than by physicians, health care facilities, and dietary supplement manufacturers. Some comments stated that certain products that did not contain ephedrine alkaloids were reported to be associated with adverse events. Several comments expressed the opinion that the AER database must be corrected to remove AERs that relate to products that do not contain ephedrine alkaloids prior to any rulemaking.

(Response) Because there is no mandatory requirement for submission of adverse event reports involving foods (including dietary supplements) to us, we rely on voluntary adverse event reporting from consumers, physicians and other health care professionals, product manufacturers, poison control centers, and State health agencies as a monitoring tool in our identification of potentially serious public health concerns that may be associated with a particular ingredient, product, or type of product. As with other passive surveillance systems, we acknowledge that voluntarily submitted adverse event reports do not always include adequate descriptions of the event and important elements of medical history, such as preexisting illness or other therapy. Our concerns about the risks of dietary supplements containing ephedrine alkaloids are based primarily on the known pharmacological effects of sympathomimetics and clinical studies using botanical and/or synthetic ephedrine alkaloids. Based on these pharmacological effects, we have identified a likelihood of potentially fatal arrhythmias, increased mortality in heart failure, and an increased rate of the consequences of elevated blood pressure, such as heart attack, stroke, and death. All of these events have been reported to be associated with consumption of dietary supplements containing ephedrine alkaloids. Because these events also occur spontaneously, specific occurrences of the events generally cannot be definitively attributed to dietary supplements containing ephedrine alkaloids, although they are compatible with the expected effects of these products. The AERs were, thus, only one component of our evaluation, which primarily relied on review of the best available scientific literature, such as peer-reviewed controlled clinical trials. The AERs are consistent with events expected from ephedrine alkaloids based on known pharmacological effects and other evidence in the scientific literature, and the AERs support our findings concerning the risks of dietary supplements containing ephedrine alkaloids.

a. *Definitional issues.*

(Comment 46) Some comments argued that only ''life-threatening'' adverse events should have been considered as the basis for the rulemaking. Another comment pointed out that a ''serious event'' is described in FDA's publication entitled ''Clinical Impact of Adverse Event Reporting'' (Ref. 32) as an event that is fatal, life-threatening, permanently/significantly disabling, requires or prolongs hospitalization, causes a congenital anomaly, or requires intervention to prevent permanent impairment or damage. The comment stated that any event that fails to meet any of these criteria must then be nonserious, reasonable, or insignificant. The comment also pointed out that an ''adverse effect'' is an unwanted effect and does not necessarily imply ''serious.'' The comment further stated that we should define key terms, including ''serious,'' ''unreasonable,'' ''significant,'' ''adverse effect,'' and ''side effect.''

Several comments also noted that the vast majority of complaints received by Metabolife International were mild and common. As such, one comment stated that some of the complaints were more accurately termed ''side effects,'' not ''adverse events.'' One Metabolife International consultant who reviewed the call records noted that there is no FDA guidance to define ''significant effect.''

(Response) We do not agree that we should consider only ''serious'' or ''life-threatening'' adverse events in our evaluation of AERs for dietary supplements containing ephedrine alkaloids. In considering reports of adverse effects of ephedra, we have focused on the reports themselves and their implications, not how they were designated. Thus, a report of tachycardia, not necessarily serious in itself, indicates a sympathomimetic response that in some patients could be dangerous. Marked increases in blood pressure would have similar implications and could suggest greater sensitivity to sympathomimetic effects in particular individuals. Reports of serious events like stroke, death or ventricular tachycardia are important, of course, but as noted earlier, can be difficult to interpret outside of a controlled trial or epidemiologic investigation. Concerns about ephedra arise principally because it has effects known to put particular individuals at risk (those with coronary artery disease or heart failure) or to pose a risk to any individual with continued use (increased blood pressure). Nonserious events that suggest sympathomimetic effects of ephedra are therefore important and need evaluation.

There is no real distinction between side effects and adverse effects. In either case, they are unwanted effects of the product. The description of the reported event is what is critical. Although we agree that the term ''adverse effect'' means there is an unwanted effect and does not necessarily imply that the event is serious, that does not mean it is insignificant. Such effects could be indicative of more serious cardiovascular risks if use of the product is continued. When considered with the scientific literature and other data, the less clinically significant effects may provide evidence that the use of a dietary supplement or dietary ingredient presents a significant or unreasonable risk of illness or injury.

In the case of dietary supplements containing ephedrine alkaloids, our evaluation indicates that serious adverse cardiovascular effects (*e.g.*, heart attack, stroke, worsened heart failure) can be expected to occur with the use of these products by the general population. Such events are relevant even if they may be expected to occur because they are known to be related to a substance, or combination of substances, contained in the product. Under section 402(f)(1)(A) of the act, a dietary supplement is adulterated if it presents a significant or unreasonable risk of illness or injury based on the conditions of use in its labeling (or under ordinary conditions of use if the labeling is silent). Therefore, if the labeled use of a dietary supplement containing ephedrine alkaloids would be expected to result in a risk of illness or injury, we must consider that risk in evaluating whether the dietary supplement is adulterated. For these reasons, we

considered all types of adverse events associated with the use of dietary supplements containing ephedrine alkaloids, even those that would not be considered ''serious'' or ''life-threatening.''

(Comment 47) Some comments stated that the AERs were anecdotal and by their nature do not allow for statistical evaluation. Other comments stated that AERs cannot establish a causal relationship between ephedra use and adverse events. Some comments cited the RAND report as support for the view that a causal relationship has not been shown.

Many comments stated that, without a control group, it is impossible to predict the number of persons who could experience the same type of adverse events that occur in the population not exposed to the product. Several comments argued that we may be detecting coincidental adverse events, which could have occurred whether or not consumers used an ephedrine alkaloid-containing dietary supplement. Many comments also stated, and pointed out that we have stated, that AERs cannot be used to calculate incidence rates of adverse events (i.e., the expected rate of adverse events occurring in the population using a product) because the actual number of persons exposed to the product is unknown, as is the actual number of adverse events that occur with use of these products.

(Response) As noted in the comments, the rate of occurrence of serious adverse events associated with a particular product or substance cannot be calculated based simply on the number of adverse events reported. Furthermore, we agree that the RAND report did not conclude that a causal relationship between ephedra and the reported adverse events had been shown. Despite the limitations of AERs, however, they can be of value in an evaluation of whether a dietary supplement presents a significant or unreasonable risk. Such reports can be important as signals of potential problems. Moreover, they can be more or less persuasive as to the strength of association between exposure to a product and occurrence of an event, depending, in part, on how likely the event is in the general population in the absence of the product. Thus, spontaneous reports have repeatedly signaled the ability of drugs to cause hepatic injury (*e.g.*, bromfenac, troglitizone) because the events seen were rarely witnessed in the absence of hepatotoxic drug or viral illness (which could be ruled out). Similarly, spontaneous reports have shown drug-caused torsade de pointes-type arrhythmias, which are also rare in the population. For more common events (*e.g.*, stroke, heart attack, headache), single reports may be harder to interpret. As previously discussed, the AERs for dietary supplements containing ephedrine alkaloids are consistent with events expected based on the scientific evidence, and the AERs support our findings.

(Comment 48) One comment urged us to disregard an e-mail memorandum from Dr. Paul Shekelle (Ref. 118) of the RAND Corp. that responds to our questions about the level of scientific proof that supports a causal relationship between the use of ephedrine-containing products and serious adverse events. The comment maintained that the opinions expressed in the e-mail are speculative, not objective, and not consistent with the peer-reviewed findings of the RAND report. The comment expressed concerns that we and others will interpret the e-mail as an extension or interpretation of the RAND report.

(Response) We are not treating the e-mail by Dr. Shekelle as an extension or interpretation of the RAND report. In seeking information from Dr. Shekelle, we were attempting to clarify the basis for RAND's conclusion regarding evidence of a causal relationship between dietary supplements containing ephedrine alkaloids and serious adverse events. We do not consider the Shekelle e-mail and Dr. Shekelle's subsequent publication (Ref. 119) as influencing the validity or interpretation of the RAND report, which is the document on which we rely.

(Comment 49) Several comments objected that we did not consider ''denominator data'' in our evaluation. Several comments stated that when the number of AERs we received is compared to the number of units sold and the population of users, the incidence of injury is insignificant or below the threshold for spontaneous illness (*e.g.*, the incidence of an adverse event in the general population) and that the level of risk is acceptable. Several related comments argued that if we made a statistical comparison of the number of AERs to the number of servings used, we could find the number of AERs to be statistically insignificant. Several comments made such a statistical comparison. For example, one comment estimated the annual number of servings of dietary supplements containing ephedrine alkaloids based on its own sales figures and an estimate of their share of the market, and concluded that the 800 AERs represent one adverse event occurring with every 8 million servings. The comments concluded that if the AER rate is statistically insignificant, the risk would be considered to be ''insignificant'' under the act.

Several comments requested that we consider industry evidence of the safe use of dietary supplements containing ephedrine alkaloids. Several of these comments were from manufacturers and distributors of dietary supplements containing ephedrine alkaloids that discussed the AERs their companies had received. One comment stated that the number of serious adverse events that the company received was statistically insignificant. Other manufacturers and distributors claimed that they had not received reports of adverse events related to the use of their dietary supplements containing ephedrine alkaloids when the products were used according to labeled directions or that lawsuits had not been filed against them. Comments from several dietary supplement trade groups or industry committees submitted survey information about the number of users of particular products or the number of units sold for particular products and the number of adverse events that were reported during the survey. These comments indicated that there were no or few adverse events (and these were mostly of a minor nature) in contrast to the millions of doses sold.

Many comments noted the experience of firms with respect to the number of complaints or lawsuits they had received on products containing particular amounts of ephedrine alkaloids, sometimes in conjunction with particular amounts of caffeine, and labeled for use for various levels of time. Some of these comments included information on the amount of product sold or the number of people consuming the product in a specified time period.

Several comments suggested that the number of adverse events estimated from the AERs is inconsistent with international data. For example, one comment noted that the Committee on Safety of Medicine (U.K.) indicated that there were only 22 reported adverse events on a product sold in the U.K. that contains a mixture of ephedrine alkaloids and caffeine in the 40 years or more that the product has been available. Similarly, some comments noted that Danish investigators estimated that 9.6 million doses of a product containing a combination of ephedrine and caffeine had been sold in Denmark in 1991 and 1992 and that only 86 reportable adverse events, defined as reactions which necessitated stopping the therapy, had been reported to the authorities during that time, despite relatively ''high dosage levels''.

(Response) We are not persuaded that the lack, or limited numbers, of adverse events reported to a limited subset of dietary supplement manufacturers and distributors demonstrates that the use of dietary supplements containing ephedrine alkaloids is safe. In contrast to the absence or low number of AERs described in some of the comments, we have received a total of more than 18,000 AERs directly, through dietary supplement firms, and from other sources. The AERs and international data discussed by the manufacturers and distributors in their comments are consistent with other adverse event reports we have received. We note that the Danish product referred to by some comments has been withdrawn from the market for safety reasons, including serious adverse event reports documenting cardiovascular and nervous system effects (Refs. 120 and 121).

There is little doubt that dietary supplement adverse events are underreported (Ref. 20). There is no requirement that manufacturers of dietary supplements report such events to FDA. Moreover, the usual reporters of AERs, physicians, are often unaware of the events themselves or the person's history of dietary supplement use. We therefore agree with the comments that the number of AERs reported to us cannot be used to calculate incidence rates. To calculate the incidence rate of an adverse event in the general population or in a subgroup of the general population, both numerator (i.e., the number of times a specific adverse event occurred with the use of a particular product over a given time period) and denominator (i.e., the total number of persons using the product over the same time period) data are needed. For reasons described previously, the adverse events that are actually reported are likely only a small fraction of the actual number of adverse events that occur with the use of these products. In addition, we have no reliable data on the use of these products by the general population or subgroups of the population. We could not evaluate the information from industry surveys on the number of people who use dietary supplements containing ephedrine alkaloids or the number of units of these products sold because this information was in summary form only (*e.g.*, the raw data were not submitted). Therefore, we do not know the actual number of persons who have used the product. In addition, because we do not have reliable information on the actual number of adverse events occurring with these products and on the size of the population exposed to dietary supplements containing ephedrine alkaloids, we cannot calculate the rate of adverse events occurring in the population using these products (i.e., incidence rate). Although we have done rough estimates for the purpose of calculating a potential economic impact, these estimates cannot be used to determine the precise incidence rates of adverse events for dietary supplements containing ephedrine alkaloids. However, we do not believe it is necessary to calculate the incidence rate to determine that dietary supplements containing ephedrine alkaloids present an unreasonable risk. Such a determination does not require us to find actual harm, only that a product's risk of illness or injury outweighs 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.

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.5.a.i, we discuss in detail how we estimated rates of adverse event reporting for purposes of our impact analysis for this final rule.

(Comment 51) One comment stated that, despite underreporting, incomplete reports, and inadequate staff, there is no credible evidence that our reporting system makes errors in detection of adverse event signals. The comment asserted the validity of an association between AERs and risks presented by ephedrine alkaloids. The comment argued that this conclusion is confirmed by the known pharmacology of ephedrine alkaloids and the types of reports seen in ephedrine clinical trials and with drugs that have a similar pharmacological action. The comment noted that 26 percent of the reports over a four-year period documented dechallenge and 4 percent documented positive rechallenge, providing additional evidence supporting causation.

(Response) We agree that our spontaneous reporting system detected the potential health risks associated with dietary supplement products containing ephedrine alkaloids and that these health risks are consistent with those documented in the scientific literature and with the known pharmacology of these products. As stated in the July 1999 GAO report entitled ''Uncertainties in Analyses Underlying FDA's Proposed Rule on Ephedrine Alkaloids'' (Ref. 124), AERs surveillance can be important as an early alert to potential problems.

In considering the comments that disputed our estimates of adverse event reporting rates, it is important to note that we are not relying on the number of AERs for dietary supplements containing ephedrine alkaloids to demonstrate quantitatively that these products present an unreasonable risk. Rather, we are relying on the AERs as supportive evidence of the risks. Although the fact that we received many AERs for these products is relevant, an exact count of the number of AERs associated with consumption of dietary supplements 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 ranges listed in trade recommendations or in product labeling. In addition, we note that the ephedrine alkaloid daily dose limit recommended by AHPA (Ref. 101) is higher than the dose administered to the treatment group in Boozer *et al.* (2002), which resulted in significantly higher blood pressure measured by ABPM when compared to the placebo group.

(Comment 53) Several comments cited the 1999 GAO report (Ref. 124) to support their criticisms of our the June 1997 proposal. These comments state that GAO criticized the validity of serious AERs reported for ephedra, particularly when used according to trade recommendations.

(Response) We do not agree that the July 1999 GAO report found the serious AERs reported for ephedra to be invalid (Ref. 124). Although the July 1999 GAO report criticized our use of adverse event reports to support the serving size and duration of use limits in the June 1997 proposal, it also emphasized that the adverse events reported to us were serious enough to warrant FDA's further investigation of the safety of dietary supplements containing ephedrine alkaloids. In addition, the report concluded that scientific information indicates that ephedrine alkaloids can affect the cardiovascular and nervous systems, citing (among others) published case reports that suggest ephedrine alkaloids can increase blood pressure in persons with normal and high blood pressure; predispose certain individuals to tachycardia (rapid heart rate), and cause cardiomyopathy (disease of the heart muscle), stroke, or myocardial necrosis (death of cells in the heart). The 1999 GAO report also noted that adverse events associated with dietary supplements containing ephedrine alkaloids include effects on the central nervous system, such as mania, paranoid psychoses, and seizures.

GAO's 2003 testimony before the Subcommittee on Oversight and Investigation of the House Committee on Energy and Commerce discussed and updated some of GAO's findings from its 1999 report on dietary supplements containing ephedrine alkaloids and provided new information, including an evaluation of Metabolife International's records of health-related calls from consumers of Metabolife 356 (Refs. 23 and 24). The 2003 GAO testimony 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 pharmacological and physiological effects of ephedrine alkaloids. The 2003 GAO testimony noted that despite the limited information contained in most of the call records, approximately 14,684 call records contained reports of at least one adverse event among consumers of Metabolife 356. The 2003 GAO testimony identified 92 serious events that included heart attacks, strokes, seizures, and deaths and emphasized that these findings were similar to other reviews of the call records, including those done by Metabolife International and its consultants. The 2003 GAO testimony noted that, in those call records where age was documented, many of the serious adverse events occurred in relatively young consumers, with more than one-third of such adverse event occurring in individuals under the age of 30. Furthermore, for those call records in which quantity of use and/or frequency and duration of use were noted, most of the serious adverse events occurred among Metabolife 356 users who used the product within the recommended guidelines, i.e., they did not take more of the product nor consume it for a longer period of time than the product label recommended. These findings are consistent with our evaluations of AERs that 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 alkaloids provide a statistically significant increase in short-term weight loss compared to placebo of about 2 pounds per month for up to 6 months.

(Response) We agree that the RAND report found evidence that supported an association between short-term use of ephedrine, ephedrine plus caffeine, or dietary supplements containing ephedrine alkaloids with or without botanicals containing caffeine and a statistically significant increase in short-term weight loss compared to placebo. RAND found that combinations of

botanical ephedrine alkaloids plus botanical sources of caffeine, or synthetic ephedrine plus caffeine, were more effective in promoting short-term weight loss than ephedra or ephedrine alone. The RAND report concluded that ephedrine alkaloid containing products, in combination with caffeine, resulted in a modest weight loss of approximately two pounds per month greater than that with placebo over a period of 4 to 6 months.

We also agree that this modest weight loss effect may be perceived as a benefit by consumers who seek to lose weight for nonhealth related purposes (*e.g.*, to look slimmer). We do not agree, however, that these studies demonstrate the long-term weight loss necessary to provide health benefits. While the improvements in obesity/overweight and the accompanying risk factors may be demonstrated in as few as 1 to 2 months, the improvements must be maintained for years to achieve a reduction in risk (Refs. 66, 126, 127, and 128). We note that dietary supplements cannot be lawfully marketed for the treatment of obesity, a disease with serious health consequences. From a health perspective, the goal of weight loss is to prevent the substantial morbidity and mortality associated with overweight and obesity (Refs. 66, 129, and 130). Obesity itself adversely impacts multiple cardiovascular risk factors, or comorbidities, including hypertension, dyslipidemia (high cholesterol), and insulin resistance with glucose intolerance. Clinical studies have demonstrated improvements in these risk markers with even modest sustained weight loss (i.e., approximately 5 to 10 percent of initial body weight). Clinical studies have also demonstrated that both the weight loss and the improvements in the comorbidities take time to accrue (i.e., months) and that, as a rule, weight is regained and the comorbidities worsened when the intervention, pharmacological or behavioral, is discontinued. Thus, interventions necessary for successful weight maintenance must be long term. As discussed in greater detail below in the response to comment 56 of this document, the reasonably well-documented moderate, short-term weight loss from use of ephedrine alkaloids, with or without caffeine, does not prevent or decrease substantial, obesity-related irreversible morbidity and mortality. We have not found evidence that demonstrates long-term weight loss with these products.

We note that, to the extent these comments raise the issue of safety, we address those issues in section V.B of this document.

(Comment 55) A number of comments from manufacturers, distributors, industry experts, and trade groups were critical of the methodology used for the RAND report or the conclusions of this review. One comment stated that RAND does not take a sufficiently quantitative approach in its review of the data in contrast to the review performed by CANTOX. The comment also objected that RAND did not perform an efficacy comparison for ephedra-caffeine and that its dose-response assessment excludes the medium dosage range (40 to 90 mg), which includes the 6-month Boozer *et al.* (2002) study. Consequently, the comment argued that these omissions preclude any assessment of the degree of agreement or disagreement between RAND and CANTOX.

Other comments objected to RAND's criteria for study inclusion in the evaluation process, stating that RAND failed to consider all relevant and applicable trials. In particular, one comment criticized RAND's decision to consider only human weight loss trials that lasted at least 8 weeks, noting that 20 of 46 identified studies were excluded for this reason, and an additional six studies for other ''alleged'' reasons. Several comments objected to RAND's conclusions that weight loss research on ephedra, ephedrine, and caffeine (6-month data) is ''short-term'' only and not sufficient to demonstrate long-term weight loss, and cited additional studies to support this view. One comment stated that 6 months is longer than the period of time recommended by FDA's Advisory Review Panel on OTC Miscellaneous Internal Drug Products with respect to evaluating weight loss ingredients used in OTC drugs. The comment stated that, by these standards, RAND's 6-month weight loss efficacy data ''exceeds the scientific requirement for evaluating OTC weight loss drugs recommended by FDA's advisory panel by 3 months.'' Other comments stated that, from a scientific perspective, there is no reason to believe the weight loss from dietary supplements containing ephedrine alkaloids would cease after a 6-month period (Refs. 70, 79, and 131).

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

We have reviewed the additional studies cited in the comments to support the effectiveness of dietary supplements containing ephedrine alkaloids for long-term weight loss (Refs. 68, 79, and 131). The results of the Filozof study have been presented only in abstract form and, therefore, neither details of the protocol nor data were available for review. The Daly *et al.* study enrolled only 24 subjects for 8 weeks in a placebo-controlled trial. After that period, 8 subjects were followed in an open label study for varying durations (1 subject was followed for 26 months). These additional studies were not evaluated in the RAND assessment because they did not meet RAND's screening criteria, and we find these studies to be either irrelevant or inadequate to change the conclusions stated in the RAND report. Therefore, we find that the Boozer 2002 study remains the longest (6-month) placebo-controlled study using ephedrine alkaloids. Consequently, we agree with RAND's conclusion that there are no studies showing an effect of dietary supplements containing ephedrine alkaloids on weight loss for more than 6 months.

Concerning the comment that referenced the Advisory Review Panel on OTC Miscellaneous Internal Drug Products with respect to evaluating weight loss ingredients used in OTC drugs, we note that the 1979 report of this panel was discussed in an advance notice of proposed rulemaking published in the **Federal Register** on February 26, 1982 (47 FR 8466). Based on the standard of practice at that time, the Advisory Review Panel

recommended that non-monograph weight loss ingredients (i.e., those not classified as GRASE) be studied for a period of 12 weeks to demonstrate effectiveness.

The treatment of obesity has evolved over the past 50 or so years (Refs. 127 and 128). In the 1960s, the mainstay of obesity treatment was behavioral modification and drugs were approved for short-term treatment to ''jump start'' patients' weight loss. There was a paradigm shift in the 1990s, with the realization that obesity is a chronic disease requiring long-term treatment, both with behavior modification and long-term drug therapy, when appropriate, in addition to diet and exercise. This shift is reflected in our draft guidance published in 1996 recommending the performance of clinical trials with a minimum 12-month treatment duration (*see* FDA Draft Guidance for The Clinical Evaluation of Weight-Control Drugs, Division of Metabolic and Endocrine Drug Products, issued on September 24, 1996) (Ref. 129). Therefore, because the treatment of obesity has evolved over time, the 1982 OTC Advisory Panel recommendations do not reflect current scientific understanding of effective treatment of obesity. There are currently no GRASE OTC drug products for weight loss or management.

(Comment 56) Many comments stated that obesity is a disease with serious health consequences. Numerous comments from consumers and physicians contained personal testimonials regarding the efficacy of dietary supplements containing ephedrine alkaloids for weight loss. Several physicians noted that patients who used these products were able to achieve long-term weight loss with an overall improvement of health, including improved cholesterol levels and lower blood pressure. No data were submitted, however, to support these statements. Several comments stated that ephedrine alkaloids are an effective tool to fight obesity. Several comments expressed the view that there are health benefits from short-term weight loss. Several other comments stated that dietary supplements containing ephedrine alkaloids are as—or more—effective for weight loss than some prescription drugs (*e.g.*, amphetamine, phentermine, sibutramine, phendimetrazine). Another comment stated that the evidence suggested that ephedra/ephedrine-caffeine supplements are as effective as OTC drugs for weight management. One comment stated that other modalities used to promote weight loss are very difficult, very dangerous, or very unsuccessful.

A comment by an industry trade group stated that the amount of weight loss identified by RAND for dietary supplements containing ephedrine alkaloids (approximately 2 pounds per month greater than placebo) is similar to that reported for approved obesity drugs (citing Ref. 128). Further, the comment asserted that ''similar to ephedra-containing supplements, there is no long-term information [on weight loss] for any but the two most recently approved drugs [sibutramine and orlistat]'' and that few studies of drugs approved for weight loss have extended to 6 months or beyond. One comment stated that double-blind placebo-controlled studies, including Boozer *et al.* (2002) (Ref. 49) have addressed the safety and efficacy of the dietary supplements containing ephedrine alkaloids, and further stated that the low cost of these products is beneficial, especially for low income groups where maintenance of a good diet is a challenge.

In contrast, other comments from physicians and medical societies, while acknowledging the results of the RAND report showing modest, but statistically significant short-term weight loss, questioned such a weight loss effect in light of the risks of these products. One comment indicated that this modest degree of ''drug-induced weight loss'' has never been shown to reduce the increased morbidity observed in obese patients. Several comments stated that there is no evidence for efficacy or safety of chronic treatment with ephedra. One medical association stated that the very modest benefits of ephedra combined with caffeine on short-term weight loss are far outweighed by the adverse effects observed in the clinical trials and the serious risks reported with the use of dietary supplements containing ephedrine alkaloids.

Several other comments, including those from an herbalist association and an herbal product manufacturer, stated that the use of these supplements, although effective, is not a sensible or healthy approach to long-term, sustainable weight management. The comment from the herbalist association also stated that obesity, with its higher risk for cardiovascular disease, is more likely to be a contraindication rather than an indication for the use of ephedra. A comment from a medical association said that NIH guidelines for the pharmacological treatment of adult obesity state that herbal preparations, including ephedra-containing products, are not recommended as part of a weight-loss program (Ref. 66).

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

(Response) As stated previously, we agree that obesity is a disease with serious health consequences; however, as some comments noted, treatment of a disease is outside the scope of the uses authorized for dietary supplements under DSHEA. Consequently, although dietary supplements containing 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 (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 previously, 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 remainder of these drugs with indications for short-term use should be withdrawn is beyond the scope of this rulemaking. The rationale for requiring

long-term studies (1 to 2 years) to evaluate drugs intended to treat obesity was thoroughly discussed in the 1995 FDA/Center for Drug Evaluation and Research (CDER) Endocrinologic and Metabolic Drugs Advisory Committee Meeting. In that meeting, the panel discussed the duration of trials for evaluating both efficacy and safety of drugs for the treatment of obesity and used the example of Fluoxetine as a drug that demonstrated efficacy for weight loss at 6 months but did not promote additional weight loss or maintain previous weight loss in longer term (1-year) studies, although the risk for experiencing adverse effects still persisted.

Alleged economic benefits of these products are not considered as a component of our evaluation of their risks and benefits. Therefore, comments suggesting an economic benefit from using dietary supplements containing ephedrine alkaloids as an alternative to drugs for weight loss are not relevant to whether dietary supplements containing ephedrine alkaloids present an unreasonable risk. We also note that there are currently no stimulant-containing OTC drugs (including those with phenylpropanolamine) legally marketed for weight management and that amphetamine is no longer labeled for weight loss. There are no existing final OTC drug monographs for any weight control drug products, although one nonstimulant ingredient (benzocaine) remains to be evaluated for this use as part of FDA's OTC drug review and can continue to be marketed pending the outcome of that review.

The comments that mentioned health benefits from short-term weight loss submitted no data to support this contention, and we are not aware of any studies that indicate any meaningful health benefit from short-term weight 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) 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 containing ephedrine alkaloids shared the opinion that the effectiveness of ephedrine alkaloids ''to support one's diet'' has been demonstrated in numerous studies, involving hundreds of patients in well-controlled environments, and that efficacy has also been demonstrated by extensive use data in the United States and Denmark. A comment from a medical association stated that, in Denmark, ephedrine is available to treat obesity, but only by prescription. Another comment stated that the Danish ephedrine-caffeine product (Letigen) has been banned and withdrawn from the market because of safety issues.

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

2. Enhancement of Athletic Performance

(Comment 58) Several comments discussed the effects of ephedrine alkaloids on athletic performance. One comment noted that, while RAND states that ephedrine is a good surrogate for evaluation of dietary supplements containing ephedrine alkaloids, RAND does not make this extrapolation for athletic performance. Many other comments stated that there are few data to support the use of synthetic ephedrine alkaloids, and no data to support the use of dietary supplements containing ephedrine alkaloids to enhance athletic performance. Therefore, these comments do not consider the enhancement of athletic performance to be an appropriate use for dietary supplements containing ephedrine alkaloids. According to some comments, RAND concluded that there are insufficient data to support use for enhancement of athletic performance. One comment asserted that any effect on athletic performance is more likely due to the caffeine in ephedrine-caffeine dietary supplements. According to another comment, the few studies that have assessed the effect of ephedrine for this use support a modest effect of ephedrine plus caffeine on very short-term (1 to 2 hours after a single dose) athletic performance in a highly selected, physically fit population, but no studies have assessed the effect of dietary supplements containing ephedrine alkaloids.

(Response) We generally agree with these comments. The RAND report provides the most comprehensive, currently available review of efficacy studies for ephedrine alkaloid containing products, focusing on two popular uses of these products—athletic performance and weight loss (*see* section V.C.1 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/NEWS/ephedra/letterslist.html* (list of firms) and *http://www.fda.gov/bbs/topics/NEWS/ephedra/warning.html* (sample letter).

3. Eased Breathing

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

4. Other Uses

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

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.

(Comment 59) Most comments that articulated a view agreed with the general notion that we must consider a risk-benefit calculus to determine whether dietary supplements containing ephedrine alkaloids present an unreasonable risk, although the comments differed as to how to perform such a calculus and as to the conclusion about whether the risks of these products outweigh their benefits. Several comments agreed with our interpretation, as published in (Ref. 132), that a ''significant or unreasonable risk'' exists when a product's risks outweigh its benefits, based on the available scientific evidence, in light of the claims the product makes and in light of the products being directly sold to consumers without medical supervision. One comment from a public interest group stated that this interpretation represents a reasonable and practical interpretation of the act that offers some protection to consumers. One comment argued that this interpretation is not permissible under *Chevron U.S.A., Inc.* because we have never adopted a risk-benefit calculus in assessing the safety of foods and because the legislative history of DSHEA does not indicate any Congressional intent to establish a risk-benefit analysis for dietary supplements. The comment stated that we should determine whether risks are ''unreasonable'' without resorting to an assessment of the benefits of the product.

(Response) We agree with the comments stating that a risk-benefit calculus is appropriate to determine whether 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 suggested or recommended in the labeling, under ordinary conditions of use. The relevant analysis for evaluating an agency's interpretation of a statute is set forth in *Chevron U.S.A., Inc.* v. *Natural Resources Defense Council*, 467 U.S. 837 (1984). Under *Chevron*, the first question is whether Congress has directly spoken to the precise question at issue (Step 1). If so, the agency must implement the unambiguous intent of Congress *Id.* at 842–843. If Congress has

not directly spoken to the precise question at issue, our interpretation will be upheld as long as it is based on a ''permissible construction'' of the statute (Step 2) *Id.* at 843–844.

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

In assessing whether Congress has clearly spoken to the question at issue, a court ''should not confine itself to examining a particular statutory provision in isolation. Rather, it must place the provision in context, interpreting the statute to create a symmetrical and coherent regulatory scheme'' (*FDA* v. *Brown and Williamson Tobacco 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.''

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 benefits, a stringent burden on us to demonstrate that the product poses an unreasonable risk of injury, evidence other than consumer complaints, and valid scientific data sufficient to predict how likely an injury is to occur. (Citing *Gulf South Insulation* v. *CPSC*, 701 F.2d 1137, 1143 (5th Cir. 1983)), (citing *Aqua Slide 'N' Dive* v. *CPSC*, 569 F.2d 831, 838 (5th Cir. 1978)), the comment stated, ''[T]he ultimate question in assessing unreasonable risk is whether the record contains 'such relevant evidence as a reasonable mind might accept as adequate to support a conclusion.'" The comment acknowledged differences in the statutes, including the explicit statutory requirement in CPSA that the regulation impose the least burdensome requirement that prevents or adequately reduces the risk injury for which the rule is being issued (15 U.S.C. 2058(f)(3)(F)). The comment also cited Consumer Product Safety Commission (CPSC) case law stating that reliable evidence of the likely number of injuries is necessary to determine whether a risk is unreasonable (*Southland Mowor Co.* v. *CPSC*, 619 F.2d 499, 510 (5th Cir. 1980)).

(Response) We do not agree that our interpretation of ''unreasonable risk'' must be confined to the view reflected in the CPSC case law cited by the comment. We have concluded, based on a *Chevron* analysis, that Congress expressly intended ''unreasonable risk'' to entail a risk-benefit analysis (*see* the response to comment 59 of this document). In the alternative, if the term ''unreasonable risk'' is ambiguous, we may interpret its meaning under *Chevron.* As the comment noted, CPSA contains an extensive list of findings that the CPSC must make, based on substantial evidence, before concluding that a consumer product poses an unreasonable risk, including, for example: (1) The degree and nature of the risk of injury the rule is designed to eliminate or reduce; (2) the approximate number of consumer products, or types or classes thereof, subject to such rule; and (3) any means of achieving the objective of the order while minimizing adverse effects on competition or disruption or dislocation of

manufacturing and other commercial practices (15 U.S.C. 2058(f)(1) and (f)(3)). The requirements imposed on CPSC in the cases that the comment cited are based on the explicit requirements of CPSA. In contrast, the adulteration provision in section 402(f)(1)(A) of the act does not require that we make any such findings. Like section 402(f)(1)(A) of the act, other parts of the act that require an evaluation of unreasonable risk, such as the device classification and banning provisions, also do not require that we make the findings set forth in CPSA. Had Congress intended that FDA make specific findings such as the degree of risk of injury, it could have so directed in the act; however, it did not. Our conclusion that dietary supplements containing ephedrine alkaloids present an unreasonable risk is based upon our finding that the risks of heart attack, stroke, and death outweigh the minimal benefits conferred by the supplements. Our conclusion is consistent with Congress's express intent in section 402(f)(1)(A) of the act.

(Comment 60) One comment by a health professional group stated that unreasonable risk likely exists when there is no information that substantiates a clear therapeutic benefit or describes a predictable relationship between exposure (dose) and response, and when the appropriate product dose is not known or achievable.

(Response) We agree that unreasonable risk exists when a dietary supplement presents a risk to health, and there is no information substantiating a benefit sufficient to outweigh that risk. In this rulemaking, we base our determination that dietary supplements containing ephedrine alkaloids present an unreasonable risk under section 402(f)(1)(A) of the act on a risk-benefit analysis, finding that the risks of heart attack, stroke, and death outweigh the benefits that may result from such products. In the absence of a use that results in a benefit that outweighs the risks of these products, we conclude that all such products pose an unreasonable risk. We therefore need not determine whether an unreasonable risk exists when the precise relationship between exposure and response is not predictable or when the appropriate product dose is not known or achievable.

(Comment 61) Several comments stated that proof of causation is required to establish unreasonable risk.

(Response) We do not agree that proof of causation is required to establish unreasonable risk under section 402(f)(1)(A) of the act, and conclude that the plain meaning of the standard precludes such an interpretation. In determining whether Congress has specifically addressed the question at issue, ''courts must exhaust the traditional tools of statutory construction, including looking at the statute's text, structure, and legislative history'' (*Chevron U.S.A., Inc.* v. *FERC*, 193 F.Supp. 2d at 67). The plain meaning of the statute is the starting point for an analysis of legislative intent. The most applicable definition of the word ''risk'' in Merriam Webster's Collegiate Dictionary is ''possibility of loss or injury'' (Merriam Webster's Collegiate Dictionary, 10th ed. 1008 (2002)) (emphasis added). Black's Law Dictionary defines ''risk,'' in part, as follows: ''In general, the element of uncertainty in an undertaking; the possibility that actual future returns will deviate from expected returns. Risk may be moral, physical, or economic.'' Black's Law Dictionary, 6th ed. 1328 (1990) (emphasis added). The words ''possibility'' and ''uncertainty'' in these definitions indicates that proof of a definitive causal relationship between the product and illness or injury is not required under section 402(f)(1)(A) of the act. If Congress had intended that definitive proof that a dietary supplement causes harm be a requirement for a showing of adulteration, it would not have used the word ''risk'' in the statute, and would have instead provided that a dietary supplement is adulterated if it ''causes'' illness or injury. This interpretation is consistent with other parts of the act, as interpreted in legislative history and case law. For instance, the legislative history of the medical device banning provisions, which require a showing of ''substantial deception or an unreasonable and substantial risk of illness or injury'' states that ''[A]ctual proof of deception or injury to an individual is [not] required'' (Section 516 of the act (21 U.S.C. 360f), H. Rept. 853, 94th Cong., 2d Sess. 19 (1976)). Case law on medical device classification also supports that we need not have causal evidence of harm (*See Lake* v. *FDA*, 1989 WL 71554 (E.D. Pa.)) (upholding FDA's finding of unreasonable risk where the risks were unknown and the benefits unproven)). Therefore, we conclude that Congress has spoken clearly and unambiguously that proof of causation is not required to show that a dietary supplement presents an ''unreasonable risk'' under section 402(f)(1)(A) of the act.

Our interpretation is also consistent with other statutes that regulate public health risks, most notably TSCA (15 U.S.C. 2601 *et seq.* (1976)). TSCA authorizes the EPA to place restrictions on chemical substances if it finds that ''* * * there is a reasonable basis to conclude that the [chemical substance] presents or will present an unreasonable risk of injury to health or the environment'' (*Id.* § 2605(a)). The legislative history of this provision states:

> This standard for taking action recognizes that factual certainty respecting the existence of an unreasonable risk of a particular harm may not be possible and the bill does not require it. Further, regulatory action may be taken even though there are uncertainties as to the threshold levels of causation.

(H. 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 containing ephedrine alkaloids should be safer than drugs and should have a much higher overall benefit/risk ratio when compared to drugs.

(Response) We agree that in regulating dietary supplements, we should

consider both risks and benefits. As discussed previously in this document, we also agree that we should weigh risks and benefits when evaluating the safety of dietary supplements under the adulteration standard in section 402(f)(1)(A) of the act. With regard to the comment from the medical association, we agree in part and disagree in part. Although the comment is correct that dietary supplements are classified as foods, we do not agree that they are required to have no risks at all. Section 402(f)(1)(A) of the act provides that a dietary supplement is adulterated if it ''presents a significant or unreasonable risk of illness or injury'' (emphasis added) as labeled, not if it presents any risk at all. Accordingly, risks that are insignificant and reasonable in light of the benefits from the supplement would not render a dietary supplement adulterated. Further, we note that conventional foods are not always risk-free. With regard to the comment's statements that dietary supplements should be safer than drugs and have a higher overall benefit/risk ratio than drugs, we do not believe it is necessary to reach these issues. For purposes of this rulemaking, we are considering whether the known and reasonably likely risks of dietary supplements containing ephedrine alkaloids outweigh their known and reasonably likely benefits. It is not necessary to determine generally how the risk/benefit ratio of dietary supplements should compare to that of drugs.

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

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

Several comments argued that the harm caused by certain medical conditions—for example, obesity—is so severe as to render the unsubstantiated (in the commenter's view) risks of taking dietary supplements containing ephedrine alkaloids insignificant relative to the benefits that would accrue from use of these products. In this view, the weight loss benefit would exceed any potential risk from taking the product and the risk is not unreasonable when compared to the harm caused by obesity. Several comments cited the prevalence of obesity and an increase in obesity over time, and urged us not to take away one important tool for consumers to address the problem. Two comments cited statistics showing that 54 percent of adults are obese in the United States, that the prevalence of obesity increased by 30 percent from 1980 to 1994, and that in 1997 the Centers for Disease Control and Prevention (CDC) attributed 42 percent of deaths to conditions that typically result from obesity. One comment stated that the risks due to obesity are a greater danger than the rare incidences of stroke or heart attacks attributed to dietary supplements containing ephedrine alkaloids.

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

(Response) We have carefully reviewed the preceding comments, and note that many of these issues have been addressed in more detail in the scientific evaluation sections V.B and C of this document. Based on the scientific data and information discussed in those sections, we have concluded that dietary supplements containing ephedrine alkaloids present an unreasonable risk of illness or injury under conditions of use recommended or suggested in their labeling, or, if no conditions of use are suggested or recommended in the labeling, under ordinary conditions of use. As discussed in the responses to comments 34 and 35 of this document, even if we were to extrapolate from data demonstrating effectiveness of certain ephedrine drug products when considering the reasonably likely benefits of dietary supplements containing ephedrine alkaloids, we conclude that the known and reasonably likely risks would outweigh even such extrapolated benefits. A summary of our rationale for reaching this conclusion is presented in our analysis below.

a. *Summary of risks for dietary supplements with ephedrine alkaloids.* People who use dietary supplements containing ephedrine alkaloids are at increased risk for serious adverse events, including heart attack, stroke, and death. Susceptible individuals (*e.g.*, those with coronary artery disease or heart failure), many of whom may not know they have underlying illnesses, are at increased risk for adverse events because these products can cause abnormal heart rhythms (pro-arrhythmic effect), even when the product is ingested at recommended doses over a short course (one or a few doses). Over longer periods of use, the risk for adverse health effects to the general population, including susceptible individuals, increases further due to a sustained elevation in blood pressure. This is a characteristic effect of the sympathomimetic class of pharmacological compounds. Moreover, the results of Boozer, *et al.* (2002) demonstrate that weight loss achieved with botanical ephedrine alkaloids does not produce the expected decrease in blood pressure (Ref. 49). The risk of experiencing harmful effects from elevated blood pressure increases the longer the blood pressure remains high, and such adverse effects are likely to occur sooner in individuals with hypertension, many of whom are unaware of their illness.

b. *Summary of known and reasonably likely benefits for dietary supplements containing ephedrine alkaloids.* As discussed in the following paragraphs, we conclude, based on all available information and data reviewed in this rulemaking, that these products do not provide a meaningful health benefit. The best clinical evidence for a benefit is for weight loss, but even there the evidence supports only a modest short-term weight loss insufficient to positively affect cardiovascular risk factors or health conditions associated with being overweight or obese. Other possible benefits, such as enhanced athletic performance, enhanced energy, or a feeling of alertness, lack scientific support and/or they would provide only temporary benefits that are trivial in comparison to the risks of serious long-

term or permanent consequences like heart attack, stroke, and death.

i. *Weight loss.* As discussed previously, the RAND report provides the most comprehensive review of efficacy studies for ephedrine alkaloid containing products. The RAND report found evidence that supported an association between short-term use of ephedrine, ephedrine plus caffeine, or dietary supplements that contain ephedrine alkaloids with or without herbs containing caffeine, and a statistically significant increase in short-term weight loss compared to placebo. The RAND report concluded that products containing ephedrine alkaloids in combination with caffeine resulted in a modest weight loss of approximately 2 pounds per month more than placebo over a period of 4 to 6 months. RAND concluded that the use of ephedrine without caffeine was associated with a statistically significant increase in weight loss (1.3 pounds of weight loss per month) compared with that of placebo for up to 4 months of use. RAND identified a single trial of 3 months duration that assessed the effect of herbal ephedra versus placebo. Those in the ephedra arm lost 1.8 pounds more per month than did those in the placebo arm. We are unaware of any appropriate, well-designed studies showing an effect of dietary supplements containing ephedrine alkaloids on weight loss for more than 6 months. Such a long-term effect would be necessary to translate into health outcome improvements.

Even if there were adequate substantiation that dietary supplements containing ephedrine alkaloids produce long-term, sustained weight loss in the overweight or obese population, the long-term risks posed by these products, particularly in obese patients who may already have underlying illnesses that can be aggravated by these products (such as hypertension), remain a serious concern. We believe that physician supervision is necessary to mitigate the risks associated with the use of sympathomimetic products in the long term for weight loss and the treatment of obesity, or for any other long-term use. This is achieved in part by monitoring patients who use these products and discontinuing product use if the patient develops hypertension, experiences other adverse health effects, or fails to achieve weight loss that would justify continued exposure to the risks associated with use of the product.

People might choose to use a dietary supplement containing ephedrine alkaloids to lose weight for purposes other than to improve health (*e.g.*, to look slimmer or fit into an outfit for a special occasion), and we do not dismiss this use as without value to the individual. To achieve the result of modest weight loss, however, these products must be used over a period of months. Individuals who use these dietary supplements over a period of months for weight loss are at risk for the adverse events that can occur with both short- and long-term use of these products. These risks are greater than the modest benefits described in the RAND report.

In the case of both short-term and long-term use, any benefits of dietary supplements containing ephedrine alkaloids for weight loss are outweighed by their risks. Therefore, we conclude that dietary supplements containing ephedrine alkaloids labeled or used for weight loss present an unreasonable risk.

ii. *Enhancement of athletic performance.* The effects of synthetic ephedrine on athletic performance were assessed in seven studies that were reviewed in the RAND report. Despite the widespread marketing of products containing ephedrine alkaloids as performance-enhancers, the RAND report found no studies involving botanical ephedrine alkaloids, and very limited evidence involving synthetic ephedrine, to support the claims. Furthermore, the RAND report concluded that, ''to show even a short-term effect of ephedrine, combination with caffeine was required.'' Therefore, there is no evidence to indicate that ephedrine alone enhances athletic performance. People who use dietary supplements containing ephedrine alkaloids for athletic performance are at risk for the same serious adverse events as individuals who use these products for other indications. As discussed previously in section V.C.2, the available evidence regarding a possible benefit from these products for enhancing athletic performance is further limited: the supporting evidence all comes from studies in which synthetic ephedrine and caffeine in combination were administered to healthy males, and the modest effects shown were in the very short term only. Even if one could disregard all the gaps in the scientific evidence and assume that ephedra has the same effect on athletic performance as synthetic ephedrine in combination with caffeine, we do not consider a modest, temporary enhancement of certain aspects of athletic performance to be a benefit sufficient to outweigh the risks of dietary supplements containing ephedrine alkaloids. Therefore, we conclude that the use of dietary supplements containing ephedrine alkaloids to enhance athletic performance for any duration of use present an unreasonable risk.

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

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

There are also dietary supplements containing ephedrine alkaloids that do not make any specific claims or otherwise suggest or recommend conditions of use in their labeling. The use of such products presents the same risks and can lead to the same serious adverse events as discussed previously for weight loss and athletic performance, even if the product is

taken under ordinary conditions of use (i.e., not abused).

A dietary supplement labeled for a very temporary, episodic use might not present an unreasonable risk if there were adequate evidence that the use resulted in a health benefit sufficient to outweigh the health risks. Any new indication would still be subject to our post-market risk evaluation as to whether it could be legally marketed. Conclusions regarding the benefit of dietary supplements containing ephedrine alkaloids for nondisease claims cannot be drawn solely from studies using synthetic ephedrine for specific diseases. Although we could require labeling for dietary supplements containing ephedrine alkaloids to limit the duration of use, among other things, currently there are no data that demonstrate that dietary supplements containing ephedrine alkaloids provide a benefit to a particular population when used temporarily or episodically (in contrast to OTC ephedrine and pseudoephedrine products for disease uses).

3. Conclusion

Multiple studies demonstrate that dietary supplements containing ephedrine alkaloids, like other sympathomimetics, raise blood pressure and increase heart rate. These products expose users to several risks, including the consequences of a sustained increase in blood pressure (*e.g.* serious illnesses or injuries that include stroke and heart attack that can result in death) and increased morbidity and mortality from worsened heart failure and pro-arrhythmic effects. Although the pro-arrhythmic effects of these products typically occur only in susceptible individuals, the long-term risks from elevated blood pressure can occur even in nonsusceptible, healthy individuals. These risks are neither outweighed by any known or reasonably likely benefits when dietary supplements containing ephedrine alkaloids are used under conditions suggested or recommended in their labeling, such as for weight loss, athletic performance, increased energy or alertness, or eased breathing. Nor do the benefits outweigh the risks under ordinary conditions of use, in the absence of suggested or recommended conditions of use in product labeling. As discussed above in section V.C of this document, the best scientific evidence of benefit is for modest short-term weight loss; however, such benefit would be insufficient to bring about an improvement in health that would outweigh the concomitant health risks. The other possible benefits discussed in section V.C if this document, have less scientific support. Even assuming that these possible benefits in fact occur, such temporary benefits are also insufficient to outweigh health risks that can lead to serious long-term or permanent consequences like heart attack, stroke, and death. On the other hand, we have determined that there are benefits from the use of OTC and prescription drug products containing ephedrine alkaloids in certain populations for certain disease indications that outweigh their risks.

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

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

We considered several regulatory alternatives to this final rule. As discussed in section I.C of this document, we issued a proposed rule in 1997 that would have placed various restrictions on dietary supplements containing ephedrine alkaloids. Most of the proposed restrictions were withdrawn in 2000; only the proposed prohibition on combining ephedrine alkaloids with other stimulant ingredients and the proposed warning statement (as modified in FDA's March 2003 notice) remain. As discussed in the following paragraphs, we have reached the conclusion that those restrictions are inadequate to protect public health. In addition, we considered other regulatory alternatives presented in the comments received.

A. Warning Statement Alone

We first proposed a warning statement in the June 1997 proposal. At that time, we tentatively concluded that a warning statement was necessary to disclose material facts about the consequences of using these products, and that it would help to reduce the risk of an adverse event after use of dietary supplements containing ephedrine alkaloids (62 FR 30670 at 30703). In our March 2003 notice, we reopened the comment period to seek, among other things, comments on a revised warning statement that we were considering at that time for dietary supplements containing ephedrine alkaloids.

We received a number of comments on the proposed labeling requirements in the June 1997 proposal and on the revised warning statement in our March 2003 notice. Because we have decided to proceed under the adulteration provision in section 402(f)(1)(A) of the act rather than to require labeling for dietary supplements containing ephedrine alkaloids, these comments are moot to the extent that they discuss the substance or format of the warning statement. Nevertheless, comments regarding the sufficiency of a warning are relevant to this rulemaking.

(Comment 64) Many comments supported the use of a warning label as an effective way to protect public health, although they differed on the specific language and format of the warning. Many comments urged us to mandate strict warning labels to inform users about the potential health risks that have been reported to be associated with the use of dietary supplements containing ephedrine alkaloids. One comment stated that product labeling does influence user behavior and strongly urged us to take action in the form of issuing a mandatory warning label for all dietary supplements containing ephedrine alkaloids. Several comments stated that there was a significant decrease in the number of AERs in certain States after their respective departments of health mandated label restrictions and strong cautionary statements. A number of comments stated that the warning labels voluntarily adopted and already used 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 1 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 ephedrine alkaloids. Even if all consumers read the warnings and the warnings thoroughly describe the risks, many using these products may not be aware they have medical conditions or individual sensitivities that put them at greater risk for experiencing serious adverse effects. A full discussion of the risks to sensitive populations appears previously in the response to comment 22 of this document.

Warning labels may be beneficial when people are able themselves to identify the risk factors they have, or when evaluation by a physician prior to use can identify whether they have the risk factors and further supervision by a physician is not necessary for safe use of the product. The purpose of the physician's evaluation is to identify individuals with underlying conditions (such as heart failure or coronary artery disease) that place them at risk for serious adverse events (such as death) due to pro-arrhythmic effects. Such warnings can reduce but not eliminate the risks from episodic use of dietary supplements containing ephedrine alkaloids because not all susceptible individuals can be identified by a physician's evaluation. For example, people can have asymptomatic coronary artery disease or early heart failure that a physician would not recognize without performing tests that would usually be reserved for patients with signs or symptoms of a disease. We are not aware of a nondisease claim for which the known and reasonably likely benefits of dietary supplements containing ephedrine alkaloids would outweigh their known and reasonably likely risks when used episodically.

A warning to consult your physician before use provides even less risk mitigation for dietary supplements containing ephedrine alkaloids that are used continuously because even healthy people would experience a rise in blood pressure and, therefore, be at increased risk for heart attack, stroke, and death. At a minimum, continued physician supervision would be a necessary risk management tool. Thus, even if consumers were to heed warning labels and consult their physician, the known and reasonably likely risks of dietary supplements containing ephedrine alkaloids when used episodically or continuously would still outweigh their known and reasonably likely benefits.

The conclusion that warning statements are not adequate to protect public health is consistent with the fact that, since 1993, we have received more than 18,000 AERs (including both adverse events reported directly to FDA and the Metabolife call records). The majority of the products associated with these AERs contained directions for use and warning statements. The warning statements varied from general precautions, suggesting that consumers check with a health care professional before beginning any diet or exercise program, to more specific warning statements, including cautions that consumers not use the product if they have certain diseases or health conditions or are using certain drugs, and to stop the use of the product if they develop certain symptoms. Despite these warning statements in the product labeling of dietary supplements containing ephedrine alkaloids, we continue to receive reports of serious adverse events.

(Comment 65) Several comments compared sensitivity to ephedrine alkaloids in dietary supplements to sensitivity to food allergens. One comment expressed the opinion that the number of individuals sensitive to ephedrine alkaloids in dietary supplements is either less than, or comparable with, those individuals who suffer from food allergies. One comment argued that warning statements are effective for people who know they are sensitive to a substance, such as peanuts. The comment suggested that if warning labels are considered sufficient in this context, they should also be considered sufficient in the 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

(Comment 66) Addressing the inadequacy of a warning statement alone, many comments supported multiple restrictions (*e.g.*, dosage limits, ingredient combination restrictions, duration of use restrictions, label claim restrictions, good manufacturing practices (GMP) requirements, and warning label statements) to reduce the risk of adverse events. One comment pointed out that the frequency, severity, and the broad cross section of the

population for which there are documented adverse events support at least this level of regulation. Some comments contended that we should establish more stringent regulations. Several of these comments recommended that we ban the use of ephedrine alkaloids in dietary supplements because of the serious health hazards associated with their use and the potential for abuse and misuse of these products.

(Response) We do not agree that the restrictions recommended in these comments will eliminate the risks imposed by dietary supplements containing ephedrine alkaloids. As discussed in the response to comment 26 of this document, we are not aware of any evidence that establishes a safe dose of ephedrine alkaloids in dietary supplements. Therefore, dose limitations cannot change the unfavorable risk-benefit ratio of these products. Similarly, a requirement for a label statement recommending that consumers limit the duration of product use will not provide adequate protection because adverse events sometimes occur after the first use or in the first few days. We also do not agree that dietary ingredient restrictions, such as limiting the presence of other stimulant ingredients, will eliminate the unreasonable risk associated with the use of dietary supplements containing ephedrine alkaloids. As explained in section V.B.1 of this document, ephedrine alkaloids given alone can be expected to cause significant increases in blood pressure, although the presence of other stimulants combined with ephedrine alkaloids may increase the risks associated with use of these products. Finally, while GMP requirements may ensure consistent quality across dietary supplement products containing ephedrine alkaloids, the risks attributed to ephedrine alkaloids are due to their inherent pharmacological and physiological effects rather than the quality of their manufacture, although poor manufacturing could lead to additional risks, such as from the introduction of toxic impurities into the product.

C. Self-Regulation

(Comment 67) Other comments objected to the June 1997 proposal, arguing that no FDA action is necessary. Several of these comments recommended that we take no action but instead continue to monitor adverse events. A number of comments stated that the dietary supplement industry will self-regulate. These comments argued that several dietary supplement trade associations have reacted responsibly to the public concerns about the AERs by setting standards for the use of ephedrine alkaloids in dietary supplements for their members (Ref. 101).

(Response) We disagree with the comments that state that no FDA action is necessary because the industry will self-regulate. It is incumbent upon us to respond to the serious adverse events associated with the use of dietary supplements containing ephedrine alkaloids and other information about the risks of these products. We have been aware for several years that a number of trade associations have policies concerning the formulation and labeling of dietary supplements containing ephedrine alkaloids. These voluntary industry standards are insufficient to alter the risk-benefit ratio for these products. Despite the fact that these industry standards are in place, we continue to receive reports of clinically significant adverse events following the consumption of dietary supplements containing ephedrine alkaloids. Some of these adverse events may be due to noncompliance with those voluntary standards; however, for the reasons stated in the response to comment 39 of this document, these types of standards, even if adhered to, would be insufficient to protect consumers from the risks posed by dietary supplements containing ephedrine alkaloids.

D. More Education

(Comment 68) One comment recommended that we provide better education to the public on the public health concerns about dietary supplements containing ephedrine alkaloids.

(Response) We do not agree that educating consumers about the public health concerns related to the use of dietary supplements containing ephedrine alkaloids is an appropriate substitute for this regulation. Although we have been active in, and support, consumer education activities about these supplements, consumer education will not adequately address the risks they present. For example, many individuals who are sensitive to sympathomimetic agents, such as the ephedrine alkaloids, and are therefore at an increased risk of experiencing an adverse event, are not aware that they are at risk. Therefore, consumer education would not be expected to greatly reduce the risk of adverse events.

E. Nonbinding Guidance

(Comment 69) Several other comments recommended the issuance of nonbinding guidance providing notice to marketers as to which dietary supplements containing ephedrine alkaloids would most likely be the subject of FDA enforcement. One comment argued that a guidance document would conform to our good guidance practices (21 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 in this document, 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.

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 clinically significant adverse effects are not limited to the use of products containing high levels of ephedrine alkaloids (Refs. 109 and 134). Therefore, enforcement actions against products containing only high levels of ephedrine alkaloids would not be expected to eliminate the unreasonable risk presented by these products. We also

note that rulemaking is a more efficient regulatory mechanism than individual enforcement actions in cases where hundreds of different products on the market contain the same ingredient that presents a risk to the public health, as is the case here. Without a regulation, we would be required to establish our case de novo with witnesses in every enforcement proceeding. Multiple proceedings would require multiple witnesses and extensive discovery, and would be extremely time-consuming and burdensome for both the courts and us. However, we point out that a regulation is not necessary to find that a dietary ingredient or a dietary supplement presents an unreasonable risk.

VII. Miscellaneous Issues

A. Freedom of Choice/FDA Bias

(Comment 71) Many comments stated that our attempt to regulate dietary supplements containing ephedrine alkaloids would erode personal freedom and the public's freedom of choice, values that the comments maintained were established through the passage of DSHEA. Several comments stated that DSHEA gives the public a right to access affordable, natural, and effective dietary supplements. A number of comments alleged that we issued the June 1997 proposal because we are biased against dietary supplements. One industry comment accused us of selectively including information in the docket. Several of these comments alleged that our purpose for issuing the June 1997 proposal was to protect the business interests of the pharmaceutical industry. Several comments explained that, if access to dietary supplements for weight loss is restricted, consumers will have little choice but to use prescription drugs. Many comments from consumers stated that use of prescription drugs for weight loss is both more costly and associated with more adverse effects than use of products containing natural herbs. Many of these comments stated that dietary supplements containing ephedrine alkaloids from natural sources are safe and have no side effects. Conversely, several comments stated that the perception that supplements are natural and, therefore, safe and acceptable alternatives to prescribed medications is erroneous and that there are serious concerns about the safety and efficacy of these products.

(Response) We deny these allegations of bias against the marketing and use of dietary supplements and any allegations of protecting or favoring the pharmaceutical industry. We support access to dietary supplements that are safe, properly labeled, and in compliance with Federal law. However, we are also obligated under DSHEA to protect the public against dietary supplements that are unsafe or otherwise adulterated. Contrary to one comment's assertion, we did not base our decision on selectively chosen information; instead, we considered all information that was submitted to the relevant dockets, including more than 48,000 comments and hundreds of studies submitted by the dietary supplement industry, trade associations, academics, health professionals, scientists, public health groups, and consumer groups. Given the scientific information about the pharmacology of ephedrine alkaloids, clinical studies examining their effects, and AERs, we found that there are serious and well-documented public health risks associated with the use of dietary supplements containing ephedrine alkaloids. Therefore, our obligation under DSHEA is to take action to address such risks, particularly in light of the products' lack of health benefits.

Additionally, comments concerning the pharmaceutical industry's business interests and possible consumer use of prescription drugs are not relevant to our determination as to whether dietary supplements containing ephedrine alkaloids are adulterated under section 402(f)(1)(A) of the act. Section 402(f)(1)(A) of the act focuses exclusively on whether the dietary supplement or dietary ingredient presents a significant or unreasonable risk; consequently, arguments pertaining to other industries or other products have no bearing on whether dietary supplements containing ephedrine alkaloids are adulterated under the act.

B. Conduct of the Advisory Committee Meetings

(Comment 72) Several comments stated that we conducted the October 1995 meeting of the Working Group and the 1996 meeting of the Food Advisory Committee (the Committees) in a manner that improperly influenced their deliberations and recommendations. These comments argued that we instructed the Committee members not to consider certain data (*e.g.*, data concerning the use of ephedrine-containing OTC drug products for the treatment of asthma); misrepresented certain data (*e.g.*, data concerning the AERs and data from clinical trials on the use of ephedrine in the treatment of obesity); failed to present data that industry believed to be relevant to the evaluation (*e.g.*, number of units of products sold during the period of time the AERs were received, data regarding whether a cause and effect relationship existed between dietary supplements containing ephedrine alkaloids and the adverse events reported to us); instructed the Committee to evaluate safety using an interpretation of ''significant harm'' (i.e., either a large number of adverse events or a serious adverse event in one individual) that is not specified in DSHEA; and improperly asked the Committee to recommend action to reduce the risks associated with the use of these products.

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

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

Regarding the conduct of the Committees' meetings, those meetings were conducted in accordance with the Federal Advisory Committee Act (5 U.S.C. App. 2), FDA's implementing regulations (21 CFR part 14), and FDA guidance entitled ''Policy and Guidance Handbook for FDA Advisory Committees'' (1994) (Ref. 137). 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 on the economy of $100 million or more, adversely affecting a sector of the economy in a material way, adversely affecting competition, or adversely affecting jobs. Executive Order 12866 also classifies a regulatory action as significant if it raises novel legal or policy issues. We have determined that this final rule is a significant regulatory action as defined by Executive Order 12866 because the benefits of the rule could exceed $100 million per year and because the rule raises novel legal and policy issues.

The Small Business Regulatory Enforcement Fairness Act of 1996 (Public Law 104–121) defines a major rule for the purpose of congressional review as having caused or being likely to cause one or more of the following: An annual effect on the economy of $100 million; a major increase in costs or prices; significant adverse effects on competition, employment, productivity, or innovation; or significant adverse effects on the ability of U.S.-based enterprises to compete with foreign-based enterprises in domestic or export markets. In accordance with the Small Business Regulatory Enforcement Fairness Act, the OMB has determined that this final rule will be a major rule for the purpose of congressional review because the benefits may exceed $100 million annually.

Title II of the Unfunded Mandates Reform Act of 1995 (Public Law 104–4) requires cost-benefit and other analyses before any rule making if the rule would include a ''Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted annually for inflation) in any 1 year.'' The current inflation-adjusted statutory threshold is $113 million per year. We have estimated that the total cost of this final rule would be no more than $90 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 in the previous paragraph. 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.

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

(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 have used only those AERs that we were certain had been caused by dietary supplements containing ephedrine alkaloids. Other comments simply pointed out that some adverse events might not have been caused by dietary supplements containing ephedrine alkaloids.

Some comments suggested that our estimate of the number of adverse events based on the number of AERs was inconsistent with the results of various studies on the safety of ephedrine alkaloids, herbal ephedra, or particular dietary supplements containing ephedrine alkaloids. One comment noted that the estimated number of adverse events, particularly the estimated number of deaths, was inconsistent with data collected by the Drug Abuse Warning Network program, which is administered by the Office of Applied Studies in the Substance Abuse and Mental Health Services Administration of HHS. Some comments made similar points with respect to the inconsistency of our estimated adverse events with the lower number of adverse events reported for ephedrine alkaloid-containing products marketed in foreign countries.

Several comments suggested that our estimate of the number of adverse events was inconsistent with their personal experience. Many comments included information on the amount of the product sold or estimates of the number of people who consumed the relevant product.

A number of comments discussed adverse events that purportedly would have occurred without consumption of dietary supplements containing ephedrine alkaloids. These comments argued that we probably generated a large number of irrelevant AERs by asking consumers to report ubiquitous symptoms as adverse events that may have been caused by these products.

Some comments criticized the report that RAND prepared for HHS on the safety and effectiveness of dietary supplements containing ephedrine alkaloids because of its attention to AERs (Ref. 21). One comment argued that RAND's approach was inappropriate because GAO had previously criticized our use of the AERs in the analysis of the June 1997 proposal. Other comments supported RAND's attention to AERs. One comment argued that RAND did not

adequately account for preexisting health conditions when classifying events in the AERs as ''sentinel'' or ''possibly sentinel'' events. Other comments criticized RAND's review of the clinical studies involving ephedrine alkaloids. One comment argued that the method RAND used to determine which clinical studies to review was biased. Some comments argued that the results of RAND's review of the AERs were inconsistent with the results of RAND's review of the clinical studies because the clinical studies enrolled enough patients to uncover the types of adverse events that appear in the AERs, if ephedrine alkaloids could cause those types of events. Other comments suggested that sources other than the RAND report provide better assessments of the risks associated with dietary supplements containing ephedrine alkaloids.

Other comments addressed one or more of the other articles that we listed in the March 2003 reopening of the comment period. Many comments criticized one or more of those studies on various bases. Other comments supported one or more of those studies. One comment argued that we presented a biased list of studies because we ignored four other articles that were published at about the same time as the articles that we listed. Some comments noted that RAND said that clinical trials that they reviewed had enrolled enough patients to detect serious adverse events at rates of 1 per 1,000 or higher.

Finally, some comments addressed trends that might affect the estimated number of adverse events. Some comments addressed the apparent upward trend in the rate at which we received AERs as of 1997, which we mentioned in the proposed rule. Some comments suggested that the perceived upward trend in AERs at that time may have been caused by changes in publicity or in the methods we used to collect adverse events, rather than by changes in the number of adverse events. One comment noted that many firms had stopped making dietary supplements containing ephedrine alkaloids.

(Response) Although uncertainty remains over the exact number of adverse events that are caused by dietary supplements containing ephedrine alkaloids, we disagree that, when estimating the number of adverse events, we should use only those AERs that we or others have proven to have been caused by dietary supplements containing ephedrine alkaloids. The comments appear to suggest that we should adopt a standard of absolute proof that a dietary supplement caused an individual adverse event. However, establishing absolute proof for individual cases is very difficult for dietary supplements or most other substances other than direct poisons. It is appropriate in the case of dietary supplements containing ephedrine alkaloids to estimate the number of adverse events prevented by this rule based upon scientifically established pharmacological effects of ephedrine alkaloids and the clinical and epidemiological evidence. The RAND report used the term ''sentinel events'' to describe adverse events that involved ephedrine alkaloids and for which RAND could exclude alternative explanations for the event with ''reasonable certainty.'' If other possible causes could not be excluded, then the report classified the cases as possible sentinel events. This level of certainty is unusually high in the context of identifying a public health risk.

We also disagree that we should use only clinical studies when estimating the number of adverse events. In addition, we disagree with the comments that stated that because clinical studies find baseline rates for stroke and major cardiac events in excess of 1 per 1,000, the existing clinical evidence is sufficient to detect adverse events associated with ephedrine alkaloids. The clinical studies reviewed by RAND were not large enough to distinguish between effects of ephedrine alkaloids and the ordinary variance around the baseline. We, therefore, do not agree that existing clinical studies are sufficiently large to detect additional adverse events associated with ephedra or ephedrine. As discussed in section V.B of this document, the scientific evidence identifies the risks presented by dietary supplements containing ephedrine alkaloids. For example, a 6-month clinical study examining the efficacy and safety of ephedrine alkaloids for the treatment of obesity found a statistically significant association between treatment with ephedrine alkaloids and higher blood pressure compared to placebo (Ref. 49). Higher blood pressure tends to increase the likelihood of cardiovascular disease. Thus, the clinical evidence establishes a potential mechanism leading from the use of dietary supplements containing ephedrine alkaloids to the occurrence of serious adverse effects.

We link the findings from this clinical study and the well-known pharmacological effects of ephedrine alkaloids to adverse events to establish the likelihood that at least some adverse events reported to be associated with the use of dietary supplements containing ephedrine alkaloids were in fact caused by these products. Although not as rigorous as an epidemiological case 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 June 1997 proposal, as we discuss in the following paragraphs.

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

Ninety 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.

Second assumption

One hundred 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 comments estimated that the system had a much smaller reporting rate of 2 percent to 4 percent for nonserious adverse events. Some comments noted that we assumed a 50 percent reporting rate in our report on Eosinophilia-Myalgia Syndrome, which was an outbreak level event (Ref. 138). These comments noted that this report referred to adverse events related to a dietary supplement, L-tryptophan, which had also received significant media publicity. These comments argued that it was, therefore, a reasonable model to use for the ephedrine alkaloid situation. Some comments suggested that we revise our reporting rate assumption from 10 percent to a range of 10 percent to 50 percent.

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

(Response) In order to express the continuing uncertainty over the reporting rate, we have calculated benefits based on reporting rates of 10 percent, 50 percent, and 100 percent of sentinel and possible sentinel events. Although the reporting rate could be lower than 10 percent, the severity of 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 sum of risk reductions expected in a population, as expressed in the following example: If the annual risk of death is reduced by one in a million for each of two million people, that represents two ''statistical lives'' saved per year (two million x one in one million = two). If the annual risk of death is reduced by one in 10 million for each of 20 million people, that also represents two statistical lives saved (Ref. 140). Similarly, the estimated value of a statistical life (VSL) is based on the willingness to pay for relatively small reductions in the risk of premature death for many people summed across a population. The individual risk management decisions on which we base estimates of the VSL must reflect the budget constraints of those individuals making those decisions. However, the resulting VSL need not reflect the budget constraints of the average person. We have revised the VSL in this analysis to a range of $5 million to $6.5 million to reflect the latest estimates of this figure (68 FR 41433 through 41506, July 11, 2003).

In addition, we have revised our method of estimating the values of avoiding the other health endpoints. For nonfatal myocardial infarction (MI), we used the same procedure that we used in our analysis of the proposed rule on trans fatty acids (64 FR 62772, November 17, 1999). That method was based on estimating the sum of the medical costs, the cost of functional disability, and the cost of pain and suffering. This method assumes that someone suffering a nonfatal MI will have functional disability or pain and suffering or both in every year after the year following the MI. We estimated the loss per year to be 0.2 quality adjusted life years (QALYs) every year of life following the MI. We did not include any reduction in life expectancy due to the MI. For this rule, we based the years of disability or pain and suffering on the ages of those suffering nonfatal myocardial infarction in the RAND report (Ref. 141). RAND reported summary information on age by type of adverse event using three age categories (13 to 30, 31 to 50, and 51 to 70). We took the midpoints of the three age categories and constructed a weighted average based on the proportion of people suffering that adverse event in those categories. We then compared that age to an average life expectancy in the United States in 2001 of 77.2 years to determine the years of disability or pain and suffering or both (Ref. 142).

We used a similar procedure to estimate new values for strokes. To estimate combined functional disability and pain and suffering we used a 0.2 quality adjusted life year (QALY) loss per year after a stroke (Ref. 143). We used the same QALY losses for ''other cardiovascular'' events that we used for nonfatal MI. We were unable to find information on chronic QALY losses for acute cases of ''other neurological,'' ''seizure,'' or ''psychiatric'' adverse events. For medical costs, we used 2001 National Statistics from HCUPnet (Ref. 144). We provide summary information on these values in table 1 of this document.

(Comment 78) Some comments that discussed the background rates of expected but unexplained adverse events argued that many AERs involved people with underlying health conditions and that dietary supplements containing ephedrine alkaloids might have simply precipitated adverse events that would have occurred within a short time anyway.

(Response) As we indicated previously in this document, we have revised our estimate of the number of relevant AERs to reflect the RAND report. The definition that RAND used for sentinel events involved investigating alternative explanations and excluding them with reasonable certainty. However, the definition that RAND used for possible sentinel events included 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.*

(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.*

(Comment 80) Some comments argued that consumers would face similar or greater health risks if they switched from dietary supplements containing ephedrine alkaloids to alternative weight loss solutions, such as prescription weight-loss drugs, other dietary supplements, or weight loss surgery.

Some comments discussed what would happen if consumers stopped using dietary supplements containing ephedrine alkaloids and did not switch to equally effective alternative weight loss methods. Some comments discussed the extent and rising trend of obesity in the United States. Some comments noted that obesity increases the risk for heart attack, stroke, diabetes, and cancer. However, other comments argued that any countervailing health costs that would result if people stopped using dietary supplements containing ephedrine alkaloids to lose weight would be small or nonexistent. Some comments suggested there were no clear health benefits from the amount of weight loss that the RAND report attributed to dietary supplements

containing ephedrine alkaloids. Other comments disagreed and argued that there were clear health benefits from the amount of weight loss that the RAND report attributed to dietary supplements containing ephedrine alkaloids. One comment argued that, although people often regain weight that they lose during a diet program, people who have participated in diet programs nevertheless generally maintain lower weights than those who have not.

(Response) Subtracting the value of countervailing health effects posed by substitute products and activities from the value of the health benefits from removing dietary supplements containing ephedrine alkaloids from the market to obtain the net health benefits is consistent with our approach for estimating benefits. (For purposes of this economic impact analysis, ''health benefits'' refers to an improvement to health and is not synonymous to the ''benefits'' that we mention in our risk-benefit analysis for purposes of determining that these products present an unreasonable risk of illness or injury; ''health benefits'' are a type of ''benefit'' we consider when making an unreasonable risk determination.) Our full conceptual model of benefits is as follows: (net change in risk from the reduction in intake of ephedrine alkaloids x value per unit change in risk) + (net change in risk from substitute products and activity x value per unit change in risk) + (net change in risk from weight gain x value per unit change in risk) + (any net change in risk from the small impact on wealth from the cost of substitute products or activity x value per unit change in risk).

However, we do not have sufficient information to estimate all elements of this model. In the analysis of the June 1997 proposal , we noted one article that found that a product a firm had reformulated to remove ephedrine alkaloids had lost approximately 33 percent of its previous sales (Ref. 145). Since that time, a media report discussed another reformulated product that had greater sales than the original product (Ref. 146). Therefore, we estimate that from two-thirds to all of the consumers of these supplements would probably switch to other dietary supplements that firms market for the same purposes as dietary supplements containing ephedrine alkaloids. This implies that between one-third and none of the consumers of these products would switch to entirely different types of weight loss or performance enhancing substitutes.

Some manufacturers have already reformulated dietary supplements so that products that had contained ephedrine alkaloids now contain alternative ingredients. Some of these reformulated products contain *Citrus aurantium* L., which is a source of synephrine, and caffeine, sometimes in the form of green tea extract. *Synephrine* is a sympathomimetic agent, and these agents are a class of compounds that also includes ephedrine alkaloids. A number of other potential herbal sources of sympathomimetics probably exist. These ingredients may pose risks that are similar to those of ephedra. If consumers switched to substitute products containing these ingredients, similar health risks might be expected as those with products containing ephedrine alkaloids. Some other ingredients that have been reported in reformulated products include cocoa beans, yerba mate, cinnamon twig, and galangal.

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

Other consumers interested in weight loss may switch to meal replacements or other diet products rather than seek medical treatment. Other consumers might choose to do nothing and simply forego the weight loss they may have obtained with ephedra products. This foregone weight loss could, in theory, generate health costs. The lack of health benefits from the weight loss associated with the use of these products, however, implies that these health costs, if any, would be negligible. Finally, some consumers might choose to reduce their caloric intake or increase their caloric output through additional exercise. These consumers would obtain additional health benefits beyond eliminating the risk of adverse events associated with dietary supplements containing ephedrine alkaloids. Those who consume supplements containing ephedrine alkaloids to enhance their athletic performance and who do not switch to other dietary supplements marketed for that purpose might switch to other stimulants, including black market products containing ephedrine alkaloids or methamphetamines. These products would pose health risks equal to or greater than those of currently marketed dietary supplements containing ephedrine alkaloids.

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

v. *Risks of certain dietary supplements containing ephedrine alkaloids.*

(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.

Several comments argued that we should not treat ephedrine alkaloids in Chinese herbal formulas that are used in Chinese medicine treatment protocols the same as dietary supplement products containing ephedrine alkaloids that consumers use to lose weight or enhance athletic performance. One comment suggested that warning statements are unnecessary for herbal products that firms distribute to ''healthcare professionals,'' including members of the American Herbalists Guild. Some comments suggested that we should set different regulatory requirements for different products or product types because risks vary by product or product type.

(Response) The RAND report found little scientific agreement on the dose-response relationship for ephedrine alkaloids (Refs. 21 and 22). Therefore, we are unable to estimate the impact of exempting products from this rule based on the level of ephedrine alkaloids that they contain. As we discussed earlier in the preamble, we have determined that botanical sources of ephedrine alkaloids

in traditional Asian herbal therapies are not covered by this rule. We do not have sufficient information to estimate the impact of exempting products based on the other considerations suggested in the comments, including type of product, label warnings, or directions for use.

b. *Revised benefit estimates.* Based on the preceding discussion, we have revised our estimate of the benefits of removing dietary supplements containing ephedrine alkaloids from the market. The social benefits of removing dietary supplements containing ephedrine alkaloids from the market consist of the increase in consumer utility that would be generated by any net health benefits resulting from removing dietary supplements containing ephedrine alkaloids from the market. The following table 1 of this document provides an estimate of the number of the various types of serious adverse events that we might eliminate by removing dietary supplements containing ephedrine alkaloids from the market, along with an estimate of the utility loss prevented by that reduction. As we discussed previously, benefits could be much lower and potentially zero if the health risks posed by substitute weight loss or sports performance products, such as other dietary supplements containing sources of sympathomimetics, were comparable to the health risks posed by ephedrine alkaloids.

We convert the number of deaths prevented into a monetary estimate by multiplying by the number of deaths by the VSL. We convert the number of nonfatal events prevented into a monetary estimate by multiplying the number of nonfatal events by the value of the appropriate change in quality QALYs. Acute events that do not have clear chronic effects will generate only minimal losses in terms of QALYs. We calculated the total benefits for each class of adverse events as: (Number of deaths prevented) x ($ per fatal case); and (number of nonfatal cases prevented) x (($ per QALY x QALY loss) + medical costs per case)). The benefits for the first year would be slightly different from the benefits in every subsequent year because the effective date is 60 days after the publication date of the final rule. By convention, we calculate benefits starting from the publication date of the final rule. Therefore, the benefits in the first year will be 5/6 (or 83 percent) of the benefits of every subsequent year. To simplify the discussion, we use the benefits for every year after the first year in all summary discussions.

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

Type	Annual Number Prevented	QALY Loss Per Case	Medical Costs per Case
Death	0.7 to 1.2	NA (used VSL)	$25,742
MI (heart attack)	0.6 to 1.0	0.29	$30,586
CVA (stroke)	1.5 to 2.1	0.2	$20,898
Other Cardiovascular (*e.g.* Cardiomyopathy, Ventricular Tachycardia)	0.1 to 0.2	0.29	$30,586
Other Neurological (*e.g.* Transient Ischemic Attack)	0.1	minimal	$13,212
Seizure	0.5 to 0.9	minimal	$11,812
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 Rate ($ 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

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—Continued

Value of Avoiding Fatal Cases and QALY Losses	Adverse Event Reporting Rate ($ in millions)		
	10 percent	50 percent	100 percent
$ 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 relabeling 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 containing ephedrine alkaloids rather than whatever they perceive to be the next closest alternative is between 1

percent and 10 percent of the sales price of the dietary supplements containing ephedrine alkaloids. This range is based on the fact that some premium must exist if consumers prefer these products to alternatives. We selected 1 percent as a lower bound because we did not find any large price differences between products containing ephedrine alkaloids and those that did not contain ephedrine alkaloids. Of course, it is possible that current consumers place a much higher premium on products containing ephedrine alkaloids than consumers who have already switched to alternatives. To allow for that possibility, we selected 10 percent (a substantial premium) as the upper bound of the range. Current market prices do not provide sufficient information for a more precise estimate. This estimate of the utility loss assumes that consumers do not incorporate the expected utility losses from potential adverse events in their willingness to pay for dietary supplements containing ephedrine alkaloids. If consumers already incorporate this information in their purchasing decisions, then it would be inappropriate to compare the value of the health benefits to the estimated utility losses for consumers using willingness to pay because the willingness to pay would already account for any adverse health effects. In that case, the estimated utility loss from the removal of these products from the market would represent the full net loss of utility.

A recent article estimated that the sales of ''herbal products'' containing ephedra accounted for between 4.3 percent and 13.5 percent of the sales for all herbal products (Ref. 135). The article did not define ''herbal products,'' but it noted that their use of the phrase ''herbal products'' included products that a natural products information company had classified as ''vitamins/supplements'' and ''grocery'' items rather than as ''herbal products'' (Ref. 147). Therefore, these estimates may have included products other than dietary supplements. Another source argued that the estimates presented in the article that we discussed previously in this paragraph did not include all relevant products. The source claimed that more comprehensive data from the Nutrition Business Journal showed that the sales of products containing herbal ephedra accounted for 33 percent of the total sales of all herbal products and 7.5 percent of the total sales of dietary supplements (Ref. 148). Both of these articles apparently dealt only with products that contained herbal ephedra. Ephedrine alkaloids are also contained in a number of different plants, including *Sida cordifolia* L., and *Pinellia ternata* (Thunb.) Makino. Therefore, these articles may have underestimated the number of products that contained ephedrine alkaloids. These articles did not present actual sales figures for herbal products, dietary supplements, or products containing ephedra. However, the Nutritional Business Journal estimated that the sales of all dietary supplements and all herbal dietary supplements in 2002 were $18 billion and $4.3 billion, respectively (Ref. 149). If one assumes that ''herbal dietary supplements'' corresponds to ''herbal products,'' then total sales of dietary supplements containing ephedrine alkaloids would be $185 million to $1,419 million.

In an effort to reduce this range, we estimated the sales of these products based on a recent survey that showed that 2 million consumers used these products at some point during a given week (Ref. 150). We assumed that consumers who used these products at some point during a given week probably used the products every day during that week, because most of the labels we have examined say that the product should be taken daily, or several times per day. We also assumed that the particular week under study was 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 relabeling 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 30678 at 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. FDA's 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

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

Type of Benefit or Cost	Benefit or Cost (rounded to $ millions)
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 $230 million per year (62 FR 30678 at 30710). We discussed reduced sales because, in that analysis, we characterized a reformulated product as the same product as before reformulation for purposes of describing the impact of the proposed action (although the reformulated products would obviously not be the same as the products they replaced). We did not receive comments that would require us to change those estimates. However, we have revised the analysis to reflect the fact that the effect on accounting profit is a more appropriate way to conceptualize the potential distributional impact than reduced sales. We can use the same information that we used to estimate consumer utility losses to consider the likely effect on the profits of firms that currently produce dietary supplements containing ephedrine alkaloids. In 2001, the average accounting profit for all Fortune 500 companies was about 5 percent of revenue, and some pharmaceutical firms had profit rates as high as 19 percent of revenue (Ref. 150). Profit rates for firms in the dietary supplement industry are probably toward the low end of this scale because of the low barriers to entry for this industry. Therefore, we assume that the profit rate for dietary supplement manufacturers is about 5 percent of total sales. As we discussed previously, press accounts suggest that manufacturers that have reformulated their dietary supplements to eliminate ephedrine alkaloids have experienced declines in sales ranging from about one-third to no decline in sales. We previously estimated total sales to be $559 million to $806 million. Therefore, we estimate that sales may decrease by $0 to $269 million per year. Assuming that the profit rate is 5 percent of sales, removing dietary supplements containing ephedrine alkaloids from the market would generate accounting profit losses of $0 to $13 million per year. We classify this impact as a transfer and not a social cost because removing dietary supplements containing ephedrine alkaloids from the market would increase the profits of firms that produce and distribute substitute products. If these other firms also have an average profit rate of 5 percent of sales, then the profit gained by these companies would also equal $0 to $13 million per year.

In addition to causing a potential reduction in profits for firms currently producing dietary supplements containing ephedrine alkaloids, removing dietary supplements containing ephedrine alkaloids from the market might also generate some countervailing transfers through the elimination of insurance costs and lawsuits associated with products containing ephedrine alkaloids. Eliminating legal fees and court costs would also generate social benefits. Of course, if reformulated products were eventually found to pose health risks comparable to those found for ephedra-based products, then these effects (i.e., the elimination of insurance and legal costs) would eventually decrease to zero. A recent press report found that ephedra manufacturers or distributors have settled 33 cases since 1994 and that an additional 42 cases were pending (Ref. 152). This represents 75 cases over 9 years, or about 8 cases per year. Recent awards for cases that have gone to court have ranged from $2.5 million to $13 million (Refs. 152 and 153). The figures reported in the media for cases that were settled out of court were considerably lower. One such case was settled out of court for $25,000 (Ref. 152). If removing dietary supplements containing ephedrine alkaloids from the market eliminated 8 cases per year, then it would decrease transfer payments from firms to consumers by between $0.2 million per year, if all cases were settled out of court, and $104 million per year, if all cases were lost in court at the high end of the range of legal penalties.

One company noted in 2002 that its product-liability insurance increased by $2.1 million from 2001 to 2002 (Ref. 146). If all 30 manufacturers saw this increase in insurance premiums, then the total increase in insurance premiums would be $60 million. Some of the independent distributors might also face higher insurance rates, but we have insufficient information to estimate those costs. Insurance rates

would not necessarily increase at this same rate in the future, and they could decrease. Therefore, we will assume that this adjustment in insurance rates reflects a one-time adjustment in the perceived liability risks associated with these products. If these higher premiums were unnecessary for reformulated products, then removing dietary supplements containing ephedrine alkaloids from the market would generate a one-time reduction in private costs of $60 million. However, if reformulated products were eventually shown to pose risks comparable to those for ephedra-based products, then insurance rates might increase to a comparable level for these products.

The uncertainty ranges associated with the potential transfers of accounting profits make it impossible to estimate the impact of removing dietary supplements containing ephedrine alkaloids from the market on the firms that currently produce and distribute dietary supplements containing ephedrine alkaloids. Firms that are unable or unwilling to produce or sell substitute products would suffer losses, and firms that are able and willing to produce or sell substitutes might not suffer decreases in profits. Indeed, media reports suggest that many firms have already voluntarily withdrawn their ephedra-based products and replaced them with reformulated products to avoid the high legal and insurance costs associated with dietary supplements containing ephedrine alkaloids (Ref. 146).

6. Option Three—Require the 2003 Proposed Warning Statement

a. *Benefits of requiring the 2003 proposed warning statement comparison to removing dietary supplements.*

i. *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 the June 1997 proposal 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 ephedrine alkaloids that was sponsored by industry endorsed this perspective, as expressed in the following quote: ''As the law appropriately suggests, the FDA cannot assume responsibility for protecting the public from themselves, if they choose to use this or any other product at higher than recommended levels or otherwise misuse properly labeled products.''

The other perspective on warning statements that we discussed in the analysis of the June 1997 proposal was that adverse events that occur despite the presence of adequate warning statements represent social costs. Under this perspective, requiring a warning statement would not be a sufficient regulatory action unless it actually caused consumers to change their behavior so as to eliminate any adverse events associated with these products. Some comments supported this perspective by arguing that warning statements are inappropriate or inadequate because they probably would not significantly reduce the number of adverse events among all or some subset of consumers.

(Response) In the analysis of removing dietary supplements containing ephedrine alkaloids from the market, we concluded that removing dietary supplements containing ephedrine alkaloids from the market would generate net social benefits if consumers fail to incorporate the probability of adverse events into their demand for those products. Our assessment of the effects of a warning statement hinges on the same uncertainty. If consumers do not fully incorporate the risk of adverse events into their demand for products containing ephedrine alkaloids, and if the proposed warning label would cause at least some consumers to change their demand so as to incorporate the risk, then the warning label could reduce adverse events and generate net social benefits. The likelihood of that outcome depends on the effectiveness of current warning statements and of warning statements in general. One 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 adverse events caused by dietary supplements containing ephedrine alkaloids by 0 to 15 percent (62 FR 30678 at 30712).

(Comment 83) A number of comments addressed this estimate. One comment suggested that the estimated impact was too low and noted that a recent study showed that almost 70 percent of adults read product labels every time they use

a product. However, another comment argued that warning statements would probably be ineffective because most consumers do not read product labels. This comment noted that there is no evidence that warning labels on alcohol and tobacco products reduced consumption of those products. Other comments simply pointed out that warning statements might not eliminate all adverse events, because some consumers might not read or follow them. One comment provided a number of reasons why warning statements might be ineffective at reducing adverse events (*e.g.* many consumers do not read labels for OTC drugs and would be even less likely to do so for dietary supplements, many consumers base their usage patterns on suggestions read in magazines rather than on label information, many consumers believe consuming more of a dietary supplement makes it more effective). Another comment noted that we appeared to infer the ostensible benefit of warning statements rather than demonstrating their effectiveness through carefully conducted clinical trials. This comment also argued that warning statements would not be useful for consumers with unrecognized medical conditions that might predispose them to adverse reactions caused by ephedrine alkaloids, such as hypertension, hyperthyroidism, vascular malformations of the brain, and subclinical cardiac arrhythmias. One comment suggested that the proposed warning statement was too long to be effective. This comment claimed that the necessary print size and spacing would discourage some consumers from reading the warning statement.

(Response) These comments did not provide sufficient information to allow us to change our estimate of the effectiveness of the warning statement that we originally proposed in 1997 and revised in 2003. The comments that noted that warning statements might not eliminate all adverse events are consistent with the assumption that warning statements would eliminate 0 to 15 percent of the adverse events. The comment that noted a study that showed 70 percent of consumers read product labels every time they purchase a product did not provide a reference for that study, but the reported results are consistent with other studies. The FDA 2002 Health and Diet Survey found that 80 percent of nonvitamin/mineral supplement users reported that they used product labels to find out if there were side effects or drug interactions associated with a product or if anyone should avoid the product. A survey of consumer use of dietary supplements by Prevention Magazine found that the following percentages of herbal remedy shoppers reported looking for the following types of information: 72 percent for possible side effects; 70 percent for warnings for people not to take the supplement, *e.g.* pregnant women; 65 percent for warnings about possible interactions with prescription medicines; and 59 percent for warnings about possible interactions with OTC products (Ref. 154). However, consumers who read warning statements will not necessarily change their behavior. A 2002 recent survey of consumers who have recently taken OTC pain medications found that 84 percent read at least some of the label the first time they took a product but that 44 percent said they took more than the recommended dosage, despite the warnings on the label (Ref. 155). In general, most of the literature on warning statements has not focused on product purchase or use pattern decisions but on issues such as comprehension, awareness, and believability (Ref. 156). Some articles have found that alcohol warning statements have had little or no impact on behavior (Ref. 157). However, these results do not necessarily hold for the proposed warning statement because the effectiveness of warning statements varies with a number of considerations, including the content and format of the warning and the characteristics of the consumers reading the warning. Thus, this literature does not provide a basis for revising our assumption that the proposed warning statement will reduce adverse events by 0 to 15 percent. However, the fact that most dietary supplements already bear extensive warning statements suggests that 15 percent is probably an upper bound and that a value closer to 0 percent is probably more likely.

(Comment 84) Some comments argued that the proposed warning statement would probably have little effect on the number of adverse events because many dietary supplements that contain ephedrine alkaloids already bear warning statements. One comment argued that some existing warning statements fully and accurately describe the potential for adverse effects and thereby satisfy the objectives of the proposed warning statement. One comment argued that some existing warning statements are more complete than the proposed warning statement. However, one comment said that the proposed warning statement would probably be more effective than existing warning statements because existing warnings do not alert consumers to avoid taking multiple products containing ephedrine alkaloids at the same time.

(Response) To address these comments, we reviewed and compared the labels of forty dietary supplements containing ephedrine alkaloids that we collected between March 20 and May 30, 2001, and also compared the number of adverse reports received during the period January 2000 to January 2004 as warning labels appeared on certain dietary supplements. (Ref. 158) All of the product labels bore some sort of warning statement. Most warning statements had many of the same basic elements as the proposed warning statement. For example, most existing warnings listed various conditions under which consumers should not take the product, various conditions under which consumers should see a health care provider before taking the product, and side effects or symptoms that should lead consumers to consult with a health care provider. However, the specific content of the various elements varied quite a bit both among existing warning statements and between existing warning statements and the proposed warning statement. Some elements of the proposed warning statement were common in existing warning statements; other elements were less common. For example, none of the existing product labels carried a PDP warning statement. In contrast, most product labels carried some sort of warning for people who had previously experienced heart problems. In addition, parts of some existing warnings were more strongly worded than the corresponding parts of the proposed warning. In other cases, parts of the proposed warning were more strongly worded than the corresponding parts of existing labels. Our label comparison did not support the notion that the proposed warning statement would have no effect because it was identical to existing warning statements. The comparison did suggest that the proposed warning statement is similar in many respects to existing warning statements, and that the proposed warning statement might not reduce adverse events very much. This result is consistent with the assumption that the proposed warning statement might eliminate between 0 and 15 percent of adverse events.

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

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

b. *Revised benefit estimates.* When we revise the analysis as described previously, we obtain the estimated benefits shown in table 5 of this document. The assumption underlying the table is that the proposed warning statement would cause some proportion of consumers to incorporate the risks from dietary supplements containing ephedrine alkaloids into their demand for these products. Some proportion of those consumers (0 to 15 percent) would cease using those products, which would reduce the number of adverse events by a like percentage. The benefits would therefore be some percentage (between 0 and 15 percent) of the benefits of removing dietary supplements containing ephedrine alkaloids from the market. The results presented in table 5 of this document apply to every year after the first year. Benefits for the first year would be lower because our proposed rule would have allowed firms up to 6 months to comply with the warning statement requirements. We do not know the actual rate at which firms would come into compliance during the initial 6 months after publication of a rule finalizing the proposed warning statement requirements. To simplify the analysis, we assume that it would take 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.*

i. *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 warning statements and suggested that we clarify that our proposed warning statement would preempt any state labeling requirements.

(Response) We reviewed the labels of the 40 dietary supplements containing ephedrine alkaloids that we collected between March 20 and May 30, 2001, to investigate label size. Most labels were wrap-around adhesive labels with a minimum label size of about 7.5 square inches and an average of about 22.8 inches. Nearly all labels already bore extensive warning statements, and most of the content of the existing warning statements was distinct from the additional warning material required by some States. Therefore, we conclude that the proposed warning statements would probably have fit on most product labels. However, some dietary supplements containing ephedrine alkaloids, possibly including traditional style extracts, might have significantly smaller labels than the products that we collected. If we had adopted this option, we would have addressed this possibility in a number of ways. Firms that cannot fit the proposed PDP warning statement on the PDP if they use the normal font size would be able to use a smaller font size. Firms that cannot fit the nonPDP warning statement on the product labels could place the warning statement on any product labeling that is an integral part of the outer product packaging such that consumers may read the warning statement at the point of purchase, including the rise backing, panel extension, and outsert. In some cases, firms may already use these packaging features. These firms would simply need to revise the content of existing

labeling. In other cases, firms might need to change the style of their packaging to utilize these types of labels. Rather than changing the style of their packaging, firms could also change the size of the package to increase the label space available for the warning statement. Changing the product packaging in 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 proposal. 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.

ii. *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 labeling requirements. Another comment suggested that we set the effective date to 60 days after publication of the final rule. Some comments suggested that we base the effective date on labeling at the manufacturing site. Under this approach, we would require products leaving the manufacturing site after the effective date to bear the warning statements, but firms could continue to sell existing inventory without the warning statement after that date.

(Response) Setting the effective date to 12 months after publication of a final rule requiring the warning statement would lead to one time labeling costs of between $2 million and $5 million. Annualizing this cost over 20 years at 3 percent and 7 percent gives an annual cost that rounds to $0 million per year (i.e., less than $500,000 per year). This would also reduce benefits in the first year to $0 under the simplifying assumption that all firms would take 12 months to comply with the required warning statement.

Eliminating all costs associated with unusable label or package inventory by allowing firms to continue to sell product without the warning statement after the effective date would lead to compliance costs of $2 million to $6 million under the proposed 180 day compliance period. Annualizing this cost over 20 years at 3 percent gives an annual cost that rounds to $0 million per year (i.e., 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 per year. In our summary statements, we present the cost estimates under the 7 percent discount rate because that range includes the range of costs that we estimated under a 3 percent discount rate. However, this option would also generate additional enforcement costs because we would need some way of determining that the products that firms sell without the warning statement were actually labeled before the effective date. In addition, this revision would reduce 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 (millions)	First Year Benefits (millions)	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 that we should allow firms to use alternative methods of disseminating warning information if they dispense products that are part of a bulk decoction formula that lacks standard labeling, such as products compounded and dispensed in Chinese herbal medicine pharmacies or by ''qualified health professionals.''

(Response) According to the March 2003 notice, we proposed to allow firms to use special labeling for the nonPDP warning statement as long as consumers could read the warning statement at the point of purchase.

(Comment 90) Some comments objected to the PDP warning statement that was part of the revised warning statement that we proposed in 2003. Other comments supported the 2003 proposed PDP warning statement. Some comments suggested that we require firms to use the PDP warning statement on both the product container and the outside container or wrapper of the retail package. One comment suggested that we require firms to include the PDP warning statement in any promotional literature and advertising.

(Response) Eliminating the PDP warning statement but retaining the nonPDP warning statement would probably significantly reduce the impact of the proposed warning statement. The PDP warning statement was one of the main elements of the proposed warning statement that differed from most existing warning statements. Reducing the impact of the warning statement by eliminating the proposed PDP warning statement would reduce both the benefits and the distributive impacts of the warning label option. However, eliminating the PDP warning statement would have little impact on the overall cost of changing labels to comply with the proposed warning statement because firms would still need to change labels even if we did not require a PDP warning statement. Requiring firms to place the warning statement on both the product container and the outside container or wrapper and requiring firms to include it in any promotional literature and advertising might increase the impact of the warning statement, but would also increase the costs. The comments did not provide sufficient information to establish that the benefits from these revisions would outweigh the costs.

(Comment 91) One comment argued that the PDP for mail order dietary supplements corresponds to the front page of any product literature that a firm uses to advertise its product. This comment said that the proposed regulation would, therefore, require some firms to change their pamphlets and other material. The comment argued that such a requirement would put mail order businesses at a competitive disadvantage relative to retail businesses. The comment suggested that we allow the warning statement to appear either above the mail order form that consumers use to order the product or above the toll free telephone number that consumers call to order the product. The comment argued that these locations would be more similar to the labeling requirements for OTC drugs.

(Response) The PDP for mail order dietary supplements is defined in the same way as the PDP for supplements sold in other ways: The label that appears on the front of the product package. It does not correspond to the front page of any product literature that a firm uses to advertise its product.

(Comment 92) Some comments objected to the requirement that firms set off the warning statement in a box graphic. One comment argued that the RAND report did not support the need for a black box type of warning statement. Some comments suggested that we give manufacturers greater leeway with respect to the format of the warning statement. Other comments supported the requirement that firms set off the warning statement in a box graphic. One comment suggested that we require firms to set off the warning

statement in a brightly colored or neon box instead of in a black box.

(Response) The proposed warning statement is consistent with current research on effective warning statements. Eliminating the box graphic would probably not significantly reduce relabeling costs. However, it might reduce the visibility of the warning statement, which would reduce the distributive impacts of the rule as well as the rule's potential health benefits. We have no information establishing that colored boxes are more effective than black boxes. Depending on the background color of the label, colored boxes may reduce the color contrast between the border and the background, which would decrease visibility of the warning statement. In addition, requiring colored boxes would increase labeling costs because some existing labels are not printed in colors.

c. *Content of PDP warning.*

(Comment 93) Some comments suggested that we revise the proposed PDP warning statement in various other ways. One comment argued that there was no evidence that ''whole-herb products'' containing ephedrine alkaloids have been associated with heart attack, stroke, seizure, or death, so that the proposed PDP warning statement would be inappropriate for those products. This comment suggested that we revise the PDP statement so that it simply informs consumers that a product contains ephedrine alkaloids and directs them to a warning statement elsewhere on the label. A number of comments argued that shortening the proposed PDP warning statement would make it more effective. One comment noted that the proposed approach is inconsistent with the ''signal/refer/explain'' format used for the labeling of other hazardous products. However, one comment suggested that we add material to the PDP warning statement, rather than shortening it.

(Response) Revising the PDP warning statement for some or all dietary supplements that contain ephedrine alkaloids would have little effect on labeling costs because firms would still need to revise their labels even if we did not require a PDP warning statement. The comments did not provide sufficient information to establish that revising the PDP warning statement would increase net benefits.

(Comment 94) A number of comments raised the issue of whom we instruct consumers to contact under various conditions. The proposed PDP and nonPDP warning statements suggest that consumers contact a ''doctor'' under various conditions. Some comments suggested we use a more general phrase such as ''health care provider'' in order to include nurse practitioners and pharmacists. One comment suggested that we change ''doctor'' to ''licensed health care provider'' to include acupuncturists who are trained in traditional Chinese medicine. The comment noted that at least half of the states that regulate the practice of acupuncture include the use of herbs in the authorized scope of practice of acupuncturists. The comment also noted that herbal ephedra is used by health care providers in other disciplines, such as naturopathy and herbalism. This comment argued that it was important to protect the ability of these groups to dispense dietary supplements containing ephedrine alkaloids.

(Response) Changing the specification of the person that the proposed warning label directs consumers to contact under various conditions would have little impact on labeling costs but would affect the benefits and distributional effects of this rule. Medical doctors are probably in the best position to advise consumers on the health implications of consuming ephedrine alkaloids under various conditions, but consumers might be able to get comparable advice from some other sources, including pharmacists and other health care providers, as well as some practitioners of acupuncture, herbalism, and naturopathy. On the other hand, obtaining advice from a medical doctor is probably more costly for many consumers than obtaining advice from other potential sources. In addition, some consumers may be unwilling to seek advice from medical doctors on the use of dietary supplements for reasons other than cost. These consumers may be less likely to follow directions to contact a medical doctor than they are to follow directions to contact a broader variety of health care providers. This component of the warning statement could also have distributional effects because directing consumers to contact a medical doctor increases the demand for the services of medical doctors and reduces the demand for the services of competing health care providers. The comments did not provide sufficient information to allow us to determine that changing the specification of the person that the label directs consumers to contact would increase net benefits. The comments also did not provide enough information for us to quantify the potential distributional impact of revising this component of the label.

(Comment 95) Some comments noted that the PDP warning statement implied that ephedrine alkaloids cause heart attack, stroke, seizure, and death. These comments argued that this is misleading because no one has proven that ephedrine alkaloids cause these types of adverse events. One comment suggested that if we refer to these types of adverse events in the warning statement, then we should include a qualifying statement explaining that no one has established a causal link between these types of adverse events and ephedrine alkaloids. This comment also suggested that we indicate in the warning statement that reports of serious adverse events are extremely rare.

(Response) Although the information in the proposed warning statement is factually correct because some people have reported the specified adverse events after consuming ephedrine alkaloids, some consumers might interpret the phrase ''have been reported'' to mean that a proven causal relationship exists between the consumption of the ephedrine alkaloids and the reported adverse events. This perception could generate additional costs in terms of lost consumer utility because some consumers who would choose not to consume these products if a proven causal relationship existed might choose to continue to consume these products if a causal relationship were only possible or even likely. One way to reduce potential misperceptions would be to add a disclaimer to the label, explaining that the causal relationship between ephedrine alkaloids and these adverse events may be uncertain. This additional material might either decrease or increase the demand for these products, and consumers are generally less likely to respond to a longer, qualified warning statement, than to a shorter, non-qualified warning statement. The comments did not provide sufficient information to establish that adding this type of clarification to the warning would increase the benefits of the warning statement.

d. *Content of nonPDP warning statement.*

(Comment 96) A number of comments suggested that we revise the proposed nonPDP warning statement. Some comments suggested that we use the same warning statement that appears on OTC drug products containing ephedrine alkaloids. One comment suggested that we allow firms to use the OTC warning statement for dietary supplements that they sell directly to health professionals for subsequent sale to consumers. One comment argued that the warning statement should not instruct consumers to contact a doctor if they experience nausea because nausea is not likely to be a precursor symptom

of a potentially serious or life-threatening condition.

Some comments objected to the warning that the risk of serious side effects increases with duration of use. One comment suggested that the scientific data showed that adverse effects dramatically decline with continued use. Some comments argued that there was no persuasive evidence that ephedrine alkaloids had any cumulative effect on the cardiovascular or central nervous systems.

One comment suggested that we allow manufacturers to add contraindications beyond those listed on the required warning label. One comment suggested that we require a statement clarifying that we have not reviewed the product for safety or efficacy. Some comments argued that we should require warning statements to include the toll free telephone number and Web site address for our MedWatch program. Some comments recommended that we require firms to indicate the amount of ephedrine alkaloids present in a product on the product label.

(Response) These comments did not provide sufficient information to analyze the costs and benefits of revising the proposed nonPDP warning statement according to their recommendation.

e. *Conclusions on benefits and costs of modifying the proposed warning statement or requiring it only for certain products*. Requiring a warning statement for certain products only would reduce costs and distributional effects and might reduce benefits compared with Option 3 (all comparisons in this section are with Option 3). Eliminating the PDP warning statement or 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

(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 argued that even if someone were to establish that ephedrine alkaloids increased cardiovascular risk by raising blood pressure, someone would still need to do a controlled research study to determine whether that effect outweighed the reduction in cardiovascular risk resulting from any weight loss generated by these products. One comment argued that a retrospective case control study is the correct study design for rare events. This comment argued that someone could do multiple studies of this type because they are quick, relatively inexpensive, and because the population exposure level is relatively high at 1 percent, according to a multistate survey on reported use of ephedra products from 1996 to 1998. Some comments suggested that we not take regulatory action until we determine that the adverse events that we suspect are caused by these supplements are due to ephedrine alkaloids rather than due to inconsistent and inaccurate formulations.

Some comments argued that we do not need to generate additional information because we already have sufficient information to remove dietary supplements containing ephedrine alkaloids from the market or require warning statements. Other comments argued that we do not need to generate additional information because we already have sufficient information to establish that these restrictions are unnecessary. Some of these comments argued that Morgenstern *et al.*, which was published after the RAND report, was just the type of case control study that the RAND report recommended (Ref. 136). These comments noted that this study found that ephedra did not raise the risk for hemorrhagic stroke. However, other comments argued that this study found that ephedra did raise the risk for hemorrhagic stroke. Some comments criticized various aspects of that study. A number of comments argued that the only additional studies that would be worthwhile to perform at this point would be unethical. These comments suggested that a human subjects committee would not allow a prospective study of the safety of ephedrine alkaloids without medical screening. They also suggested that a cohort study would be difficult because ephedrine alkaloids do not generate significant health benefits and also because of the ethical requirements to effectively inform participants of the risks.

(Response) Generating additional information might reduce the remaining uncertainty associated with the benefits of this rule or it might not. Generating additional information may be difficult, time consuming, and expensive. In addition, it is not clear that reducing the remaining uncertainty would change the outcome of this rulemaking. The comments did not provide sufficient information to allow us to estimate the costs and benefits of delaying rulemaking until we generate additional information.

(Comment 98) Other comments suggested that we should take some type of action other than issuing a regulation or generating additional information. A number of comments suggested that we address any problems with dietary supplements containing ephedrine alkaloids by using our existing authority to seize unsafe or adulterated dietary supplements. Other comments suggested that we address any problems by using our existing authority to investigate and prosecute unscrupulous multilevel marketing (MLM) distributors. Another comment suggested that we develop a level 1 guidance document rather than taking regulatory action.

(Response) The comments did not provide sufficient information to establish that spending additional

resources on enforcement of existing regulations or on promulgating a level 1 guidance document would generate greater net benefits than issuing this final rule. Following guidance documents 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. Benefit-Cost Analysis: Summary

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

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

Option	Annual Cost	Annual Benefit	Net
1. Take no new regulatory action (baseline)	$0	$0	$0
2a. Remove dietary supplements containing ephedrine alkaloids from the market (if consumer behavior does not already incorporate risk)	$7 to $90	$43 to $132	- $47 to $125
2b. Remove dietary supplements containing ephedrine alkaloids from the market (if consumer behavior already incorporates risk)	$7 to $90	$0	- $90 to - $7
3. Require 2003 warning atatement	$0 to $1	$0 to $20	- $1 to $20
4. Require warning statement, but modify it or require only on certain products	NA	NA	NA
5. Generate additional information or take some action other than removal or warning statements	unknown	unknown	unknown

B. Small Entity Analysis

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

(Comment 99) Some comments addressed our estimate of the number of small firms in the analysis of the proposed rule. Some comments argued that we had ignored a large number of independent small distributors in the analysis of the proposed rule. One comment suggested we revisit our analysis of the impact of the rule on small businesses. One comment

suggested we obtain information on the impact of the rule on small entities by opening a dialogue with industry associations.

(Response) We have revisited and revised our estimate of the number of firms based on a database of dietary supplement products that the Research Triangle Institute compiled under contract to FDA after publication of the proposed rule. This database listed 30 firms associated with 48 dietary supplement products containing ephedrine alkaloids (Ref. 159). To estimate the number of these firms that are small, we used a database of dietary supplement manufacturing practices that was also compiled by RTI under contract to FDA (Ref. 160). This database had size information for only a few of the 30 firms that we identified as relevant from the first database. Therefore, we estimated the number of small firms based on the percentage of all dietary supplement firms in the database that would qualify as small firms. The Small Business Administration (SBA) publishes definitions of small businesses by the North American Industry Classification System (NAICS) code. The firms in the database fell into the following NAICS codes: (1) 311222 Soybean Processing, (2) 311920 Coffee and Tea Manufacturing, (3) 325188 All Other Basic Inorganic Chemical Manufacturing, (4) 325199 All Other Basic Organic Chemical Manufacturing, (5) 325411 Medicinal and Botanical Manufacturing, and (6) 325412 Pharmaceutical Preparation Manufacturing. SBA defines small businesses in these NAICS codes based on a maximum number of employees, as follows: 311222 and 311920—no more than 500 employees; 325411 and 325412—no more than 750 employees; and 325188 and 325199—no more than 1000 employees. The database of firms listed 1,566 individual plants and 146 parent companies. Essentially all individual plants qualified as small businesses (98 percent under a maximum of 500 employees and 100 percent under a maximum of 1,000 employees). However, approximately 12 percent of the individual plants were associated with parent companies, and only about half of the parent companies qualified as small businesses (53 percent under a maximum of 500 employees and 58 percent under a maximum of 1,000 employees). Based on this information, we estimated that about 94 percent of the 30 firms associated with dietary supplement containing ephedrine alkaloids, or about 28 firms, would qualify as small businesses.

There may also be a number of independent distributors that are not captured in our database of dietary supplement firms. All or most of these firms would probably qualify as small businesses. However, we do not have sufficient information to estimate the number of distributors or to compare their characteristics to the SBA definition of a small business for that industry. As we noted in the previous paragraphs, this final rule will generate shifts in demand that might adversely affect these firms. However, the most likely substitutes for dietary supplements containing ephedrine alkaloids are other dietary supplements, and the same distributors that handle dietary supplements containing ephedrine alkaloids might also handle these other dietary supplements. Therefore, the net distributive impact on small distributors may be small or nonexistent. Although demand shifts generated by this final rule might also increase business for other small businesses, we do not consider countervailing positive effects on other small entities when assessing the impact of our rules on small entities.

In response to the request that we open a dialogue with industry associations, we note that small entities, and trade associations (with member small entities) submitted a number of comments regarding small business impact during the various comment periods for this rulemaking.

In the preceding cost-benefit analysis, we estimated that removing dietary supplements containing ephedrine alkaloids from the market would generate annualized cost of $1 million to $9 million over 20 years because of the need to reformulate products. This would correspond to a cost per firm across 30 firms of between $30,000 and $300,000 per year. In addition, we estimated that profits might be reduced by $0 to $13 million per year due to decreased sales. Profits may accrue to either manufacturers or distributors. If all profit losses affected manufacturers only, then the annual profit loss per firm across 30 firms would be between $0 and $ 430,000, which would give a total cost per firm of $30,000 to $730,000. Most of these firms are small, so even $30,000 per year (the lower bound) would be a significant additional burden. We previously estimated total sales to be $559 million to $806 million. If we assume that profits correspond to approximately 5 percent of sales, then annual profits would be $28 million to $40 million. If we assume that all profits accrue to manufacturers, then profits would be $0.9 million to $1.3 million per year per firm across 30 firms. In that case, reformulation costs would represent 2 percent to 33 percent of total profits, while total costs would represent 2 percent to 81 percent of total profits. The Regulatory Flexibility Act does not specify a threshold for costs to have a significant economic impact, but the 2 ranges we have calculated reach a high fraction of total profit; for some individual small firms the fraction of profit would be higher. If some of the profit losses accrued to distributors rather than manufacturers, then the potential cost per firm across all firms would be lower. However, we have insufficient information to estimate the number of distributors or the sales or profits per distributor.

(Comment 100) One comment argued that the PDP warning statement would have a significant economic impact on small businesses. This comment argued that the nonPDP warning statement would be adequate to protect consumers. This comment recommended that we eliminate the PDP warning statement.

(Response) A PDP warning statement might have a significant impact on small businesses. We have analyzed the costs of the proposed warning statement as a whole (including both PDP and nonPDP components) in our analysis of impacts under Executive Order 12866. However, the comment did not provide sufficient information to differentiate the impact on small businesses from the impact on other regulated entities, or to differentiate the impact of the PDP warning from the impact of the nonPDP warning.

(Comment 101) One comment recommended that we consider reasonable alternatives to the rule in order to reduce the burden on small businesses.

(Response) The discussion of regulatory options in the preceding benefit-cost analysis pertains primarily to small businesses because nearly all affected firms are small businesses under SBA size definitions. We could develop a definition of a very small business (different from the SBA definition of a small business) and develop additional regulatory options to reduce the burden on those firms, but those options would also be similar to those in the benefit-cost analysis. As we stated elsewhere in this analysis, any option that would reduce the regulatory burden on very small firms would also reduce benefits by increasing the risk to public health. We do not have sufficient information to compare the value of the

regulatory relief for very small firms to the associated reduction in benefits.

IX. Environmental Impact

Removing dietary supplements containing ephedrine alkaloids from the market will not have a significant impact on the human environment. Therefore, an environmental impact statement is not required.

X. Paperwork Reduction Act

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

XI. Federalism

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

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

We are aware that several States have laws concerning dietary supplements containing ephedrine alkaloids, such as required label statements, which clearly contemplate the continued marketing of such products. Section 301(a) of the act (in relevant part) prohibits the introduction or delivery for introduction into interstate commerce of any adulterated food. In this rule, the agency has declared dietary supplements containing ephedrine alkaloids to be 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, and Independent Regulatory Agencies, dated October 28, 1999) (Ref. 161). Thus, we certify that the intergovernmental consultation process described in section 4(d) of Executive Order 13132 did not occur for the proposed rule, but we also believe that State and local governments had sufficient notice and an opportunity to participate in this rulemaking process. We note that the proposed rule was subject to a previous Executive Order, Executive Order 12612, which was also entitled, ''Federalism,'' and had a similar consultation and notification obligation for federal agencies. When we issued the proposed rule, we notified the States, and State and local health departments, among others, submitted comments to the proposal (65 FR 17474, April 3, 2000) (stating that State and local health departments and government agencies had commented on the proposed rule)). Furthermore, a subsequent notice, published on March 5, 2003, expressly asked whether we should determine that dietary supplements containing ephedrine alkaloids present a ''significant or unreasonable risk of illness or injury'' under section 402(f)(1)(A) of the act (68 FR at 10417, 10419, and 10420). Although the March 2003 notice did not contain a separate Federalism analysis, we believe that States were aware of the March 2003 notice because at least five State or local governments or legislators submitted comments in response to the March 2003 notice, and most of these comments urged us to ban the sale of such products.

XII. References

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

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List of Subjects in 21 CFR Part 119

Dietary ingredients, Dietary supplements, Foods.

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

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

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

§ 119.1 Dietary supplements containing ephedrine alkaloids.

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

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

Dated: January 28, 2004.

Mark B. McClellan,

Commissioner of Food and Drugs.

Dated: February 4, 2004.

Tommy G. Thompson,

Secretary of Health and Human Services.

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