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.

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

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

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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.

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[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.

*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; 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 phenylpropanolamine 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

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[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.

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.

*D. Petitions Received Relating to Dietary Supplements 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 7). 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.

## V. 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 T. 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 oozer 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 xpressing 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 phedra, 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 phedrine, 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 y 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 lkaloids 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