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 website included anecdotal reports of individuals who reported dependence or apparent addiction associated with use of ephedrine and dietary supplements containing ephedrine alkaloids. Several other comments cited the German Commission E monograph's instructions to limit the use of ephedra preparations to short-term because of the danger of addiction. (The Commission E was a division of the German Federal Health Agency established in 1978 to evaluate the safety and efficacy of herbal medicines sold in Germany. It produced official monographs for botanicals and botanical formulations sold in German pharmacies.)

(Response) We agree that ephedrine alkaloids and amphetamines share some pharmacological and physiological properties that may be associated with abuse and dependence. Psychostimulant effects that have been reported with sympathomimetic agents include drug tolerance, dependence, or addiction, although these psychostimulant effects are better recognized for cocaine and amphetamines (Ref. 102) (English abstract (Ref. 103)). Ephedrine alkaloids exhibit physiological effects common to the amphetamines, but differ in the relative intensity of these effects. We agree that amphetamines and cocaine have been shown to have much greater reinforcing effects and higher

liability for abuse than products containing ephedrine alkaloids, but also agree that the development of dependence from the use of ephedrine alkaloids has been noted with both pharmaceutical and botanical products (Ref. 104–106). The greater possibility of dependence and abuse of amphetamine-containing and cocaine-containing drug products marketed in the United States is recognized by the placement of these substances in Schedule II of the Controlled Substances Act (CSA). Ephedrine-containing drug products are not scheduled under the CSA; however, ephedrine, its salts, optical isomers, and salts of optical isomers are List 1 chemicals under the CSA (see 21 U.S.C. 802(34)) because they are chemical precursors of methamphetamine (Schedule II) and are used in its illicit manufacture. As List 1 chemicals, these substances are subject to various DEA requirements, including recordkeeping, reporting, and sale behind the counter (see 21 CFR 1310.03–1310.07). While we are concerned about the potential for abuse, we did not rely on evidence of abuse or dependence to make our determination under section 402(f)(1)(A) of the act.

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

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

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

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

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

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

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

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

5. Traditional Asian Medicine

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

supplements, highlighting the differences in the products themselves and how they are used from what is used in traditional medicine.

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

Several comments asserted that traditional Asian medicine *Ephedra* formulae often deliver lower amounts of ephedrine alkaloids compared to other types of ephedrine alkaloid-containing products and that traditional formulae rarely contain more than 15 percent *Ephedra* in the herb mixture. Comments also asserted that *Ephedra* in traditional formulae is usually combined with other botanicals that typically modify *Ephedra*'s inherent stimulant effects. Another comment attributed the relative safety of *Ephedra* to the mixture of

ephedrine alkaloid isomers not present in purified or synthetic alkaloids. One comment suggested that the established therapeutic dose range of *Ephedra sinica* in herbal medicine formulae is 60–90 mg total alkaloids per day (adults), which falls within the dosage range established for OTC ephedrine/pseudoephedrine-containing drugs (150 mg and 240 mg alkaloids daily, respectively), and the recommendations of the Germany Commission E (maximum daily *Ephedra* alkaloid dose of 300 mg daily). Other comments asserted that infusions or teas of *Ephedra* are effective in relieving respiratory symptoms but have fewer side effects and are safer than formulations containing isolated or synthetic ephedrine alkaloids or prescription drugs. Another comment stated that supplements in a liquid tea form greatly reduce the risk of excess acute consumption by the public.

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

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

the supervision of a health care provider, is irresponsible and dangerous. A number of traditional Asian medicine practitioners maintained that many consumers experienced adverse effects because of this improper use, over-dosage, or conflict with their illnesses.

Because of these differences, many practitioners of traditional Asian medicine commented that they support our June 4, 1997 proposed rule except to the extent that it would restrict their use of *Ephedra* in traditional Asian medicine. Several comments asserted that since most serious adverse effects involve use of ephedrine alkaloids and not whole herb or whole herb extracts of *Ephedra*, any rule must exempt whole herb *Ephedra* or whole herb *Ephedra* extracts that contain no added ephedrine alkaloids. Furthermore, ephedrine alkaloid-free species of *Ephedra* should also be exempted.

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

(Response) This final rule does not affect the use of *Ephedra* preparations in traditional Asian medicine, although we considered the comments' views and information on the use of *Ephedra* in traditional Asian medicine in the

context of their possible relevance to the risks of dietary supplements containing ephedrine alkaloids. This rule applies only to products regulated as dietary supplements (see 62 FR 30678 at 30691). Traditional Asian medicine practitioners do not typically use products marketed as dietary supplements.

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

6. Adverse Events

AERs involving drugs include those submitted to us voluntarily by consumers or healthcare professionals and those submitted by manufacturers who are required to report them to us. However, there is no required reporting of AERs to us for dietary supplements, including those containing ephedrine

alkaloids. Depending on other information we may have about the event or about the suspect product, AERs can be hard to interpret. AERs may raise concerns about a product, as well as buttress a finding that a particular dietary supplement represents an unreasonable risk based on other types of evidence. Some AERs can be reasonably persuasive on their own. For example, individual cases of adverse events where dechallenge (discontinued use) and rechallenge (restarting use) have been linked to the abatement and recurrence of the events, strongly support the association between exposure to the product and occurrence of the adverse event. FDA, and others, have reviewed and analyzed the AERs in depth to add to the body of evidence and to ensure that all relevant evidence is considered (Ref. 109–115). Despite the limitations of such reports, a detailed review of the AERs submitted to us for dietary supplements containing ephedrine alkaloids and comparison of those AERs to scientific data about the pharmacology of these substances establishes that the AERs are consistent with the known and expected pharmacological effects of these products considered (Ref. 109,115,116).

In the preamble to the June 4, 1997 proposed rule, we stated that there were more than 800 reports of illnesses and injuries associated with the use of dietary supplements containing ephedrine alkaloids. Since that time, we have received more than 2,200 additional AERs submitted directly to us plus approximately 18,000 reports from call records submitted by Metabolife International, one of the largest distributors of dietary supplements containing ephedrine alkaloids. These records have been placed in the record for this rulemaking in redacted form.

A Congressional subcommittee minority report (Ref. 117), posted at *http://www.house.gov/reform/min/pdfs/pdf__inves/*

pdf__dietary__ephedra__metabolife__rep.pdf noted that the call records from Metabolife contain nearly 2,000 reports of significant AERs for its products, including 3 deaths, 20 heart attacks, 24 strokes, 40 seizures, 465 episodes of chest pain, and 936 reports of heart rhythm disturbances. In addition to these cardiac and neurological events, psychiatric symptoms were also reported. These reports include 46 reports of hospitalization following use of their products, and 82 additional reports of emergency room care. The report stated that in more than 90 percent of the most serious AERs— stroke, heart attack, seizure, and psychosis—where dosage information is documented in the call record, the consumer had followed the manufacturer's dosage recommendations. It also stated that among those most significant adverse event reports for which age was noted, 50 percent of the consumers were under 35 and many of the consumers were reported as being in good health with no prior medical problems. Despite the limited information provided in Metabolife International's call records, we note that these types of adverse events reported are consistent with the scientifically documented effects and potential risks of ephedrine alkaloids in those cases where appropriate information was available to make a medical evaluation of the reported event.

(Comment 45) Many comments criticized our system for collecting and evaluating adverse events and our use of AERs. A number of comments criticized the reporting system, stating that many of the received reports were insufficiently documented and lacked critical information necessary for appropriate evaluation. Other comments stated that the reports were anecdotal and that no scientific standards were used in their evaluation.

Several comments stated that our attempt to rely on AERs for attributing adverse events to dietary supplements containing ephedrine alkaloids is in

conflict with established scientific principles and FDA policy. The comments cited the criticism of our reliance on AERS in the July 1999 GAO Report, our bases for regulation of Yellow No. 5 which included AERs and multiple clinical studies, and the opinion that our AER review system was biased and lacked scientific rigor.

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

(Response) Because there is no mandatory requirement for submission of adverse event reports involving foods (including dietary supplements) to us, we rely on voluntary adverse event reporting from consumers, physicians and other health care professionals, product manufacturers, poison control centers, and State health agencies as a monitoring tool in our identification of potentially serious public health concerns that may be associated with a particular ingredient, product, or type of product. As with other passive surveillance systems, we acknowledge that voluntarily submitted adverse event reports do not always include adequate descriptions of the event and important elements of medical history, such as pre-existing illness or other therapy. Our concerns about the risks of dietary supplements containing ephedrine alkaloids

are based primarily on the known pharmacological effects of sympathomimetics and clinical studies using botanical and/or synthetic ephedrine alkaloids. Based on these pharmacological effects, we have identified a likelihood of potentially fatal arrhythmias, increased mortality in heart failure, and an increased rate of the consequences of elevated blood pressure, such as heart attack, stroke, and death. All of these events have been reported to be associated with consumption of dietary supplements containing ephedrine alkaloids. Because these events also occur spontaneously, specific occurrences of the events generally cannot be definitively attributed to dietary supplements containing ephedrine alkaloids, although they are compatible with the expected effects of these products. The AERs were, thus, only one component of our evaluation, which primarily relied on review of the best available scientific literature, such as peer-reviewed controlled clinical trials. The AERs are consistent with events expected from ephedrine alkaloids based on known pharmacological effects and other evidence in the scientific literature, and the AERs support our findings concerning the risks of dietary supplements containing ephedrine alkaloids.

a. *Definitional Issues.*

(Comment 46) Some comments argued that only "life-threatening" adverse events should have been considered as the basis for the rulemaking. Another comment pointed out that a "serious event" is described in the FDA publication Clinical Impact of Adverse Event Reporting (Ref. 32) as an event that is fatal, life-threatening, permanently/significantly disabling, requires or prolongs hospitalization, causes a congenital anomaly, or requires intervention to prevent permanent impairment or damage. The comment stated that any event that fails to meet any of these criteria must then be non-serious,

reasonable, or insignificant. The comment also pointed out that an "adverse effect" is an unwanted effect and does not necessarily imply "serious." The comment further stated that we should define key terms, including "serious," "unreasonable," "significant," "adverse effect," and "side effect."

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

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

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

In the case of dietary supplements containing ephedrine alkaloids, our evaluation indicates that serious adverse cardiovascular effects (e.g., heart attack, stroke, worsened heart failure) can be expected to occur with the use of these products by the general population. Such events are relevant even if they may be expected to occur because they are known to be related to a substance, or combination of substances, contained in the product. Under section 402(f)(1)(A) of the act (21 U.S.C. 342(f)(1)(A)), a dietary supplement is adulterated if it presents a significant or unreasonable risk of illness or injury based on the conditions of use in its labeling (or under ordinary conditions of use if the labeling is silent). Therefore, if the labeled use of a dietary supplement containing ephedrine alkaloids would be expected to result in a risk of illness or injury, we must consider that risk in evaluating whether the dietary supplement is adulterated. For these reasons, we considered all types of adverse events associated with the use of dietary supplements containing ephedrine alkaloids, even those that would not be considered "serious" or "life-threatening."

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

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

(Response) As noted in the comments, the rate of occurrence of serious adverse events associated with a particular product or substance cannot be calculated based simply on the number of adverse events reported. Furthermore, we agree that the RAND report did not conclude that a causal relationship between ephedra and the reported adverse events had been shown. Despite the limitations of AERs, however, they can be of value in an evaluation of whether a dietary supplement presents a significant or unreasonable risk. Such reports can be important as signals of potential problems. Moreover, they can be more or less persuasive as to the strength of association between exposure to a product and occurrence of an event,

depending, in part, on how likely the event is in the general population in the absence of the product. Thus, spontaneous reports have repeatedly signaled the ability of drugs to cause hepatic injury (e.g., bromfenac, troglitizone) because the events seen were rarely witnessed in the absence of hepatotoxic drug or viral illness (which could be ruled out). Similarly, spontaneous reports have shown drug-caused torsade de pointes-type arrhythmias, which are also rare in the population. For more common events (e.g., stroke, heart attack, headache), single reports may be harder to interpret. As previously discussed, the AERs for dietary supplements containing ephedrine alkaloids are consistent with events expected based on the scientific evidence, and the AERs support our findings.

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

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

influencing the validity or interpretation of the RAND report, which is the document on which we rely.

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

Several comments requested that we consider industry evidence of the safe use of dietary supplements containing ephedrine alkaloids. Several of these comments were from manufacturers and distributors of dietary supplements containing ephedrine alkaloids that discussed the AERs their companies had received. One comment stated that the number of serious adverse events that the company received was statistically insignificant. Other manufacturers and distributors claimed that they had not received reports of adverse events related to the use of their dietary supplements containing ephedrine alkaloids when the products were used according to labeled directions or that lawsuits

had not been filed against them. Comments from several dietary supplement trade groups or industry committees submitted survey information about the number of users of particular products or the number of units sold for particular products and the number of adverse events that were reported during the survey. These comments indicated that there were no or few adverse events (and these were mostly of a minor nature) in contrast to the millions of doses sold.

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

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

(Response) We are not persuaded that the lack, or limited numbers, of adverse events reported to a limited subset of dietary supplement

manufacturers and distributors demonstrates that the use of dietary supplements containing ephedrine alkaloids is safe. In contrast to the absence or low number of AERs described in some of the comments, we have received a total of more than 18,000 AERs directly, through dietary supplement firms, and from other sources. The AERs and international data discussed by the manufacturers and distributors in their comments are consistent with other adverse event reports we have received. We note that the Danish product referred to by some comments has been withdrawn from the market for safety reasons, including serious adverse event reports documenting cardiovascular and nervous system effects (Ref. 120,121).

There is little doubt that dietary supplement adverse events are underreported (Ref. 20). There is no requirement that manufacturers of dietary supplements report such events to FDA. Moreover, the usual reporters of AERs, physicians, are often unaware of the events themselves or the person's history of dietary supplement use. We therefore agree with the comments that the number of AERs reported to us cannot be used to calculate incidence rates. To calculate the incidence rate of an adverse event in the general population or in a subgroup of the general population, both numerator (i.e., the number of times a specific adverse event occurred with the use of a particular product over a given time period) and denominator (i.e., the total number of persons using the product over the same time period) data are needed. For reasons described above, the adverse events that are actually reported are likely only a small fraction of the actual number of adverse events that occur with the use of these products. In addition, we have no reliable data on the use of these products by the general population or subgroups of the population. We could not evaluate the information from industry surveys on the number of people

who use dietary supplements containing ephedrine alkaloids or the number of units of these products sold because this information was in summary form only (e.g., the raw data were not submitted). Therefore, we do not know the actual number of persons who have used the product. In addition, because we do not have reliable information on the actual number of adverse events occurring with these products and on the size of the population exposed to dietary supplements containing ephedrine alkaloids, we cannot calculate the rate of adverse events occurring in the population using these products (i.e., incidence rate). Although we have done rough estimates for the purpose of calculating a potential economic impact, these estimates cannot be used to determine the precise incidence rates of adverse events for dietary supplements containing ephedrine alkaloids. However, we do not believe it is necessary to calculate the incidence rate to determine that dietary supplements containing ephedrine alkaloids present an unreasonable risk. Such a determination does not require us to find actual harm, only that a product's risk of illness or injury outweighs its benefits in light of the claims and directions for use in the product's labeling or, if the labeling is silent, under ordinary conditions of use.

b. *Reporting issues, including underreporting.*

(Comment 50) Although many comments agreed that the adverse events for dietary supplements containing ephedrine alkaloids were underreported, a number of comments disagreed with our estimates in the June 4, 1997 proposed rule. Some comments believed that adverse events were less underreported than we estimated, while others thought they were more underreported. One manufacturer stated that it does not report the complaints it receives to us but rather keeps them for its own records.

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

In section xx, we discuss in detail how we estimated rates of adverse event reporting for purposes of our impact analysis for this final rule.

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

a four-year period documented dechallenge and 4 percent documented positive rechallenge, providing additional evidence supporting causation.

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

In considering the comments that disputed our estimates of adverse event reporting rates, it is important to note that we are not relying on the number of AERs for dietary supplements containing ephedrine alkaloids to demonstrate quantitatively that these products present an unreasonable risk. Rather, we are relying on the AERs as supportive evidence of the risks. Although the fact that we received many AERs for these products is relevant, an exact count of the number of AERs associated with consumption of dietary supplements containing ephedrine alkaloids is not necessary to our determination that these products present an unreasonable risk.

c. Interpretation of AERs As Supporting the Existence of Public Health Risks

(Comment 52) Several comments stated that the number of AERs does not raise a public health concern. One comment asserted that AERs with appropriate use of ephedra are rare. Other comments stated that there is no association between the use of dietary supplements containing ephedrine alkaloids and serious adverse events when used with appropriate dosages,

including the American Herbal Products Association (AHPA) trade recommendations. One comment noted that some of the AERs appear to be related to high amounts of ephedrine (i.e., in excess of 500 mg/day) and that the relationship of intake to adverse events with the use of lower amounts consumed is unknown.

(Response) We disagree with these comments. Public health concerns were initially raised by the number of AERs following consumption of dietary supplements containing, or suspected to contain, ephedrine alkaloids in comparison to the number of AERs for all other dietary supplements; the type of adverse event (e.g. cardiovascular system and nervous system effects); and the severity of the adverse events associated with the use of these products. The type, severity, and number of adverse events reported to us prompted us to investigate further. In many of these AERs, including those designated as "most significant" in the Congressional minority report (Ref. 117), the dietary supplement products were consumed as directed on the manufacturer's label. Although we do not endorse any current trade recommendations for the use of dietary supplements containing ephedrine alkaloids, we note that in many of the AERs, the amounts of ephedrine alkaloids consumed were within the ranges listed in trade recommendations or in product labeling. In addition, we note that the ephedrine alkaloid daily dose limit recommended by AHPA (Ref. 101) is higher than the dose administered to the treatment group in Boozer et al. (2002), which resulted in significantly higher blood pressure measured by ABPM when compared to the placebo group.

(Comment 53) Several comments cited the 1999 GAO report (Ref. 124) to support their criticisms of our use of AERs in the June 4, 1997 proposed rule.

These comments state that GAO criticized the validity of serious AERs reported for ephedra, particularly when used according to trade recommendations.

(Response) We do not agree that the 1999 GAO report found the serious AERs reported for ephedra to be invalid (Ref. 124). Although the July 1999 GAO report criticized our use of adverse event reports to support the serving size and duration of use limits in the June 4, 1997 proposed rule, it also emphasized that the adverse events reported to us were serious enough to warrant FDA's further investigation of the safety of dietary supplements containing ephedrine alkaloids. In addition, the report concluded that scientific information indicates that ephedrine alkaloids can affect the cardiovascular and nervous systems, citing (among others) published case reports that suggest ephedrine alkaloids can increase blood pressure in persons with normal and high blood pressure; predispose certain individuals to tachycardia (rapid heart rate), and cause cardiomyopathy (disease of the heart muscle), stroke, or myocardial necrosis (death of cells in the heart). The 1999 GAO report also noted that adverse events associated with dietary supplements containing ephedrine alkaloids include effects on the central nervous system, such as mania, paranoid psychoses, and seizures.

GAO's 2003 testimony before the Subcommittee on Oversight and Investigation of the House Committee on Energy and Commerce discussed and updated some of GAO's findings from its 1999 report on dietary supplements containing ephedrine alkaloids and provided new information, including an evaluation of Metabolife International's records of health-related calls from consumers of Metabolife 356 (Ref. 23,24). The 2003 GAO testimony noted that the types of adverse events identified in the health-related call records from Metabolife International were consistent with the types of adverse events

reported to us, as well as with the scientifically documented pharmacological and physiological effects of ephedrine alkaloids. The GAO testimony noted that despite the limited information contained in most of the call records, approximately 14,684 call records contained reports of at least one adverse event among consumers of Metabolife 356. The 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 of such adverse event occurring in individuals under the age of 30. Furthermore, for those call records in which quantity of use and/or frequency and duration of use were noted, most of the serious adverse events occurred among Metabolife 356 users who used the product within the recommended guidelines, i.e., they did not take more of the product nor consume it for a longer period of time than the product label recommended. These findings are consistent with our evaluations of AERs that we have received regarding dietary supplements containing ephedrine alkaloids (Ref. 27,109).

The 2003 GAO testimony noted that the adverse event reports are important sources of information concerning health risks of dietary supplements containing ephedrine alkaloids because the regulatory framework for dietary supplements is basically one of post-marketing surveillance and does not require pre-market approval. The testimony stressed that despite the limited information obtained from the Metabolife International call records, the types of adverse events reviewed were consistent with the known risks of

ephedrine alkaloids, including serious adverse events such as five reports of death. Finally, the testimony noted that several years earlier, we had concluded that dietary supplements containing ephedrine alkaloids present a "significant public health hazard" based upon the adverse event reports received and the consistency of those reports with the known pharmacological effects of ephedrine alkaloids.

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

1. Weight Loss

(Comment 54) Numerous comments, including those from manufacturers and industry trade groups, stated that the results of the RAND report and other evidence, including the CANTOX review and the Boozer et al. clinical studies (Ref. 49,125), support or establish the safety and efficacy of dietary supplements containing ephedrine alkaloids for weight loss. Several comments stated that RAND concludes that dietary supplements containing ephedrine alkaloids have proven benefits for weight loss purposes. Several comments stated that RAND shows that dietary supplements containing ephedrine alkaloids provide a statistically significant increase in short-term weight loss compared to placebo of about 2 pounds per month for up to 6 months.

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

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

We also agree that this modest weight loss effect may be perceived as a benefit by consumers who seek to lose weight for non-health related purposes (e.g., to look slimmer). We do not agree, however, that these studies demonstrate the long-term weight loss necessary to provide health benefits. While the improvements in obesity/overweight and the accompanying risk factors may be demonstrated in as few as one to two months, the improvements must be maintained for years to achieve a reduction in risk (Ref. 67,126–128). We note that dietary supplements cannot be lawfully marketed for the treatment of obesity, a disease with serious health consequences. From a health perspective, the goal of weight loss is to prevent the substantial morbidity and mortality associated with overweight and obesity (Ref. 67,129,130). Obesity itself adversely impacts multiple cardiovascular risk factors, or comorbidities, including hypertension, dyslipidemia (high cholesterol), and insulin resistance with glucose intolerance. Clinical studies have demonstrated improvements in these risk markers with even modest sustained weight loss (i.e., approximately 5 to 10 percent of initial body weight). Clinical studies have also demonstrated that both the weight loss and the improvements in the comorbidities take time to accrue (i.e., months) and that, as a rule, weight is regained and the comorbidities worsened when the intervention, pharmacological or behavioral, is discontinued. Thus, interventions necessary for successful weight maintenance must be long term. As discussed in greater detail below in the response to comment 56, the reasonably well-documented moderate, short-

term weight loss from use of ephedrine alkaloids, with or without caffeine, does not prevent or decrease substantial, obesity-related irreversible morbidity and mortality. We have not found evidence that demonstrates long-term weight loss with these products.

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

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

Other comments objected to RAND's criteria for study inclusion in the evaluation process, stating that RAND failed to consider all relevant and applicable trials. In particular, one comment criticized RAND's decision to consider only human weight loss trials that lasted at least 8 weeks, noting that 20 of 46 identified studies were excluded for this reason, and an additional 6 studies for other "alleged" reasons. Several comments objected to RAND's conclusions that weight loss research on ephedra, ephedrine, and caffeine (6-month data) is "short-term" only and not sufficient to demonstrate long-term

weight loss, and cited additional studies to support this view. One comment stated that 6 months is longer than the period of time recommended by FDA's Advisory Review Panel on OTC Miscellaneous Internal Drug Products with respect to evaluating weight loss ingredients used in OTC drugs. The comment stated that, by these standards, RAND's 6-month weight loss efficacy data "exceeds the scientific requirement for evaluating OTC weight loss drugs recommended by FDA's advisory panel by 3 months." Other comments stated that, from a scientific perspective, there is no reason to believe the weight loss from dietary supplements containing ephedrine alkaloids would cease after a 6-month period (Ref. 71,80,131).

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

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

We have reviewed the additional studies cited in the comments to support the effectiveness of dietary supplements containing ephedrine alkaloids for long-term weight loss (Ref. 69,80,131). The results of the Filozof study have been presented only in abstract form and, therefore, neither details of the protocol nor data were available for review. The Daly et al study enrolled only 24 subjects for 8 weeks in a placebo-controlled trial. After that period, 8 subjects were followed in an open label study for varying durations (1 subject was followed for 26 months). These additional studies were not evaluated in the RAND assessment because they did not meet RAND's screening criteria, and we find these studies to be either irrelevant or inadequate to change the conclusions stated in the RAND report. Therefore, we find that the Boozer 2002 study remains the longest (6-month) placebo-controlled study using ephedrine alkaloids. Consequently, we agree with RAND's conclusion that there are no studies showing an effect of dietary supplements containing ephedrine alkaloids on weight loss for more than six months.

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

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

(Comment 58) Many comments stated that obesity is a disease with serious health consequences. Numerous comments from consumers and physicians contained personal testimonials regarding the efficacy of dietary supplements containing ephedrine alkaloids for weight loss. Several physicians noted that patients who used these products were able to achieve long-term weight loss with an overall improvement of health, including improved cholesterol levels and lower blood pressure. No data were submitted, however, to support these statements. Several comments stated that ephedrine alkaloids are an effective tool to fight obesity. Several comments expressed the view that there are health benefits from short-term weight loss. Several other comments stated that dietary supplements containing ephedrine alkaloids are as—or more—effective

for weight loss than some prescription drugs (e.g., amphetamine, phentermine, sibutramine, phendimetrazine). Another comment stated that the evidence suggested that ephedra/ephedrine-caffeine supplements are as effective as OTC drugs for weight management. One comment stated that other modalities used to promote weight loss are very difficult, very dangerous, or very unsuccessful.

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

In contrast, other comments from physicians and medical societies, while acknowledging the results of the RAND report showing modest, but statistically significant short-term weight loss, questioned such a weight loss effect in light of the risks of these products. One comment indicated that this modest degree of "drug-induced weight loss" has never been shown to reduce the increased morbidity observed in obese patients. Several comments stated that there is no evidence for efficacy or safety of chronic treatment with ephedra. One medical association stated that the very modest benefits of ephedra combined

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

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

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

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

ephedrine alkaloids could, if they did not present an unreasonable risk of illness or injury, be labeled for ordinary weight loss, they are subject to regulation as drugs if promoted for the treatment of obesity. See 65 FR 1000 at 1026–27 (January 6, 2000). We agree with the comments stating that obesity should be treated only with drugs that have been approved as safe and effective for that use.

We do not agree with the comments comparing the effectiveness of dietary supplements containing ephedrine alkaloids for weight loss to approved prescription drugs. The drugs mentioned by the comments are approved for the treatment of obesity, which is a use for which dietary supplements cannot be marketed. Furthermore, we are unaware of any data that have made direct comparisons between dietary supplements containing ephedrine alkaloids for weight loss and drugs approved for the treatment of obesity. As discussed above, prescription drugs for the treatment of obesity are no longer approved on the basis of short-term data or for short-term use. Of note, the few prescription drugs that were approved for short-term use to 'jump-start' weight loss are all stimulants and are controlled substances, the first group being approved in 1939 (amphetamine) and the last being approved in 1979 (phendimetrazine). The use of the majority of these drugs has fallen out of favor or the drugs have been withdrawn from the U.S. market. Whether the remainder of these drugs with indications for short-term use should be withdrawn is beyond the scope of this rulemaking. The rationale for requiring long-term studies (1 to 2 years) to evaluate drugs intended to treat obesity was thoroughly discussed in the 1995 FDA/CDER Endocrinologic and Metabolic Drugs Advisory Committee Meeting. In that meeting the panel discussed the duration of trials for evaluating both efficacy and safety of drugs for the

treatment of obesity and used the example of Fluoxetine as a drug that demonstrated efficacy for weight loss at 6 months but did not promote additional weight loss or maintain previous weight loss in longer term (one year) studies, although the risk for experiencing adverse effects still persisted.

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

The comments that mentioned health benefits from short-term weight loss submitted no data to support this contention, and we are not aware of any studies that indicate any meaningful health benefit from short-term weight loss. In the longest controlled study to date on the effect of ephedrine alkaloid containing products on weight loss by Boozer et al. (2002) (Ref. 49), subjects treated with placebo, plus diet and exercise recommendations, lost an average of approximately 6 pounds over a period of 6 months. (Ref. 49) Subjects treated with a proprietary blend of herbal ephedra and kola nut (a source of caffeine), plus diet and exercise recommendations, lost an average of approximately 12 pounds during the same time period. As described above in the response to

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

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

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

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

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

2. Enhancement of Athletic Performance

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

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

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

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

We determined that certain labeling claims made by manufacturers of dietary supplements containing ephedrine alkaloids for athletic performance enhancement were unsubstantiated in light of the findings in the RAND report. These claims were the subject of warning letters sent to various manufacturers in February and March 2003 (available at *http://www.fda.gov/bbs/topics/NEWS/ephedra/letterslist.html* (list of firms) and *http://www.fda.gov/obs/topics/ NEWS/ephedra/warning.html* (sample letter).

3. "Eased Breathing"

We are aware that there are teas and other types of dietary supplements containing ephedrine alkaloids marketed with claims such as "eased breathing" or "better breathing." We are not aware, however, of any adequately substantiated benefit from the use of these products. There are no data that support a benefit to breathing from dietary supplements containing ephedrine alkaloids in healthy people. Moreover, because healthy people are able to

breathe without difficulty, we do not believe there is any respiratory benefit in the absence of a disease state (e.g., asthma or a respiratory infection). We note that claims to treat or mitigate a disease, or the effects of a disease, subject a product to regulation as a drug under the act.

4. Other Uses

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

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

1. What does "unreasonable risk" mean?

A threshold issue is the legal standard of "significant or unreasonable risk of illness or injury" (section 402(f)(1)(A) of the act). By its plain language, this standard requires evidence of "significant or unreasonable risk of illness or injury" (emphasis added)." There is no requirement that there be evidence conclusively demonstrating causation of actual harm in specific individuals.

In our evaluation of "significant or unreasonable risk," we can consider any relevant evidence, including scientific data about the toxicological properties of a dietary ingredient or its mechanisms of action; scientific information about the well-known effects of pharmacologically-related compounds, including those regulated as drugs; the results of clinical studies, including observational studies; and adverse event reports that have been subject to sound scientific analysis. The government's burden of proof for "significant or unreasonable risk" can be met with any science-based evidence of risk, without the need to prove that the substance has actually caused harm in particular cases.

Thus, a dietary supplement that caused a sustained rise in blood pressure across the population would increase the risk of cardiovascular events including stroke, heart attack, or death to that population. Even risks that may not be detectable in small studies or studies of short duration could, over time, and on a population-wide basis, result in hundreds or thousands of adverse events. The government's burden of proof for "unreasonable risk" is met when a product's risks outweigh its benefits in light of the claims and directions for use in the product's labeling or, if the labeling is silent, under ordinary conditions of use.

(Comment 59) Most comments that articulated a view agreed with the general notion that we must consider a risk-benefit calculus to determine whether dietary supplements containing ephedrine alkaloids present an unreasonable risk, although the comments differed as to how to perform such a calculus and as to the conclusion about whether the risks of these products outweigh their benefits. Several comments agreed with our interpretation, as published in (Ref. 132), that a "significant or unreasonable risk" exists when a product's risks outweigh its benefits, based on the available scientific

evidence, in light of the claims the product makes and in light of the products being directly sold to consumers without medical supervision. One comment from a public interest group stated that this interpretation represents a reasonable and practical interpretation of the act that offers some protection to consumers. One comment argued that this interpretation is not permissible under *Chevron* because we have never adopted a risk-benefit calculus in assessing the safety of foods and because the legislative history of DSHEA does not indicate any Congressional intent to establish a risk-benefit analysis for dietary supplements. The comment stated that we should determine whether risks are "unreasonable" without resorting to an assessment of the benefits of the product.

(Response) We agree with the comments stating that a risk-benefit calculus is appropriate to determine whether dietary supplements containing ephedrine alkaloids present an unreasonable risk of illness or injury under conditions of use recommended or suggested in the labeling, or if no conditions of use are suggested or recommended in the labeling, under ordinary conditions of use. The relevant analysis for evaluating an agency's interpretation of a statute is set forth in *Chevron v. Natural Resources Defense Council*, 467 U.S. 837 (1984). Under Chevron, the first question is whether Congress has directly spoken to the precise question at issue (Step 1). If so, the agency must implement the unambiguous intent of Congress. *Id.* at 842–43. If Congress has not directly spoken to the precise question at issue, our interpretation will be upheld as long as it is based on a "permissible construction" of the statute (Step 2). *Id.* at 843–44.

In determining whether Congress has specifically addressed the question at issue, "courts must exhaust the traditional tools of statutory construction,

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

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

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

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

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

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

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

In the absence of explicit standards for the evaluation of "unreasonable risk," one comment urged us to be guided by precedent from other agencies. The comment highlighted the Consumer Product Safety Act (CPSA), its implementing regulations, and related case law. The comment stated that any assessment of "unreasonable risk" must include a balancing of risks and benefits, a stringent burden on us to demonstrate that the product poses an unreasonable risk of injury, evidence other than consumer complaints, and valid scientific data sufficient to predict how likely an injury is to occur. Citing *Gulf South Insulation v. CPSC*, 701 F.2d 1137, 1143 (5th Cir. 1983) (citing Aqua *Slide 'N' Dive v. CPSC*, 569 F.2d 831, 838 (5th Cir. 1978)), the comment stated, "'[T]he ultimate question in assessing unreasonable risk is whether the record contains 'such relevant evidence as a reasonable mind might accept as adequate to support a conclusion.'" The comment acknowledged differences

in the statutes, including the explicit statutory requirement in the CPSA that the regulation impose the least burdensome requirement that prevents or adequately reduces the risk injury for which the rule is being promulgated. 15 USC 2058(f)(3)(A). The comment also cited Consumer Product Safety Commission (CPSC) case law stating that reliable evidence of the likely number of injuries is necessary to determine whether a risk is unreasonable. *Southland Motor v. CPSC*, 619 F.2d 499, 510 (5th Cir. 1980).

(Response) We do not agree that our interpretation of "unreasonable risk" must be confined to the view reflected in the CPSC case law cited by the comment. We have concluded, based on a *Chevron* analysis, that Congress expressly intended "unreasonable risk" to entail a risk-benefit analysis (see the response to comment 59). In the alternative, if the term "unreasonable risk" is ambiguous, we may interpret its meaning under *Chevron*. As the comment noted, the CPSA contains an extensive list of findings that the CPSC must make, based on substantial evidence, before concluding that a consumer product poses an unreasonable risk, including, for example: the degree and nature of the risk of injury the rule is designed to eliminate or reduce; the approximate number of consumer products, or types or classes thereof, subject to such rule; and any means of achieving the objective of the order while minimizing adverse effects on competition or disruption or dislocation of manufacturing and other commercial practices. 15 U.S.C. § 2058(f)(1) & (3). The requirements imposed on CPSC in the cases that the comment cited are based on the explicit requirements of the CPSA. In contrast, the adulteration provision in section 402(f)(1)(A) of the act does not require that we make any such findings. Like section 402(f)(1)(A) of the act, other parts of the act that require an evaluation of unreasonable risk, such as the device classification

and banning provisions, also do not require that we make the findings set forth in the CPSA. Had Congress intended that FDA make specific findings such as the degree of risk of injury, it could have so directed in the act; however, it did not. Our conclusion that dietary supplements containing ephedrine alkaloids present an unreasonable risk is based upon our finding that the risks of heart attack, stroke, and death outweigh the minimal benefits conferred by the supplements. Our conclusion is consistent with Congress's express intent in section 402(f)(1)(A) of the act.

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

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

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

(Response) We do not agree that proof of causation is required to establish unreasonable risk under section 402(f)(1)(A) of the act, and conclude that the plain meaning of the standard precludes such an interpretation. In determining whether Congress has specifically addressed the question at issue, "courts must exhaust the traditional tools of statutory construction, including looking at the statute's text, structure, and legislative history." *Chevron v. FERC*, 193 F.Supp.2d at 67. The plain meaning of the statute is the starting point for an analysis of legislative intent. The most applicable definition of the word "risk" in Merriam Webster's Collegiate Dictionary is "*possibility* of loss or injury." Merriam Webster's Collegiate Dictionary, 10th ed. 1008 (2002) (emphasis added). Black's Law Dictionary defines "risk," in part, as follows: "In general, the element of uncertainty in an undertaking; the possibility that actual future returns will deviate from expected returns. Risk may be moral, physical, or economic." Black's Law Dictionary, 6th ed. 1328 (1990) (emphasis added). The words "possibility" and "uncertainty" in these definitions indicates that proof of a definitive causal relationship between the product and illness or injury is not required under section 402(f)(1)(A) of the act. If Congress had intended that definitive proof that a dietary supplement causes harm be a requirement for a showing of adulteration, it would not have used the word "risk" in the statute, and would have instead provided that a dietary supplement is adulterated if it "causes" illness or injury. This interpretation is consistent with other parts of the act, as interpreted in legislative history and case law. For instance, the legislative history of the medical device banning provisions, which require a showing of "substantial deception or an unreasonable and

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

Our interpretation is also consistent with other statutes that regulate public health risks, most notably TSCA. 15 U.S.C. § 2601 *et seq.* (1976). TSCA authorizes the Environmental Protection Agency (EPA) to place restrictions on chemical substances if it finds that "there is a reasonable basis to conclude that the [chemical substance] presents or will present an unreasonable risk of injury to health or the environment." Id. § 2605(a). The legislative history of this provision states, "This standard for taking action recognizes that factual certainty respecting the existence of an unreasonable risk of a particular harm may not be possible and the bill does not require it. Further, regulatory action may be taken even though there are uncertainties as to the threshold levels of causation." H.R. Rep. No. 94–1341, 94th Cong., 2d Sess. 23 (1976).

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

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

One comment by a medical association stated that, because dietary supplements are classified as foods, and therefore are assumed to be safe, it is imperative that such products have no risks and provide some benefit to consumers. More specifically, the comment stated that dietary supplements containing ephedrine alkaloids should be safer than drugs and should have a much higher overall benefit/risk ratio when compared to drugs.

(Response) We agree that in regulating dietary supplements, we should consider both risks and benefits. As discussed previously, we also agree that we should weigh risks and benefits when evaluating the safety of dietary supplements under the adulteration standard in section 402(f)(1)(A) of the act. With regard to the comment from the medical association, we agree in part and disagree in part. Although the comment is correct that dietary supplements are classified as foods, we do not agree that they are required to have no risks

at all. Section 402(f)(1)(A) of the act provides that a dietary supplement is adulterated if it "presents a *significant* or *unreasonable* risk of illness or injury" (emphasis added) as labeled, not if it presents any risk at all. Accordingly, risks that are insignificant and reasonable in light of the benefits from the supplement would not render a dietary supplement adulterated. Further, we note that conventional foods are not always risk-free. With regard to the comment's statements that dietary supplements should be safer than drugs and have a higher overall benefit/risk ratio than drugs, we do not believe it is necessary to reach these issues. For purposes of this rulemaking, we are considering whether the known and reasonably likely risks of dietary supplements containing ephedrine alkaloids outweigh their known and reasonably likely benefits. It is not necessary to determine generally how the risk/benefit ratio of dietary supplements should compare to that of drugs.

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

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

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

Several comments argued that the harm caused by certain medical conditions—for example, obesity—is so severe as to render the unsubstantiated (in the commenter's view) risks of taking dietary supplements containing ephedrine alkaloids insignificant relative to the benefits that would accrue from use of these products. In this view, the weight loss benefit would exceed any potential risk from taking the product and the risk is not unreasonable when compared to the harm caused by obesity. Several comments cited the prevalence of obesity and an increase in obesity over time, and urged us not to take away one important tool for consumers to address the problem. Two comments cited statistics showing that 54 percent of adults are obese in the United States, that the prevalence of obesity increased by 30 percent from 1980–94, and that in 1997 the Centers for Disease Control and Prevention (CDC) attributed 42 percent of deaths to conditions that typically result from obesity. One comment stated that the risks due to obesity are a greater danger than the rare incidences of stroke or heart attacks attributed to dietary supplements containing ephedrine alkaloids.

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

risk for serious adverse events exists and that RAND concluded that an assessment of case reports is insufficient to reach conclusions regarding causality.

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

a. *Summary of Risks for Dietary Supplements With Ephedrine Alkaloids.* People who use dietary supplements containing ephedrine alkaloids are at increased risk for serious adverse events, including heart attack, stroke, and death. Susceptible individuals (e.g., those with coronary artery disease or heart failure), many of whom may not know they have underlying illnesses, are at increased risk for adverse events because these products can cause abnormal heart rhythms (pro-arrhythmic effect), even when the product is ingested at recommended doses over a short course (one or a few doses). Over longer periods of use, the risk for adverse health effects to the general population,

including susceptible individuals, increases further due to a sustained elevation in blood pressure. This is a characteristic effect of the sympathomimetic class of pharmacological compounds. Moreover, the results of Boozer, et al. (2002) demonstrate that weight loss achieved with botanical ephedrine alkaloids does not produce the expected decrease in blood pressure (Ref. 49). The risk of experiencing harmful effects from elevated blood pressure increases the longer the blood pressure remains high, and such adverse effects are likely to occur sooner in individuals with hypertension, many of whom are unaware of their illness.

b. *Summary of Known and Reasonably Likely Benefits for Dietary Supplements Containing Ephedrine Alkaloids.* As discussed below, we conclude, based on all available information and data reviewed in this rulemaking, that these products do not provide a meaningful health benefit. The best clinical evidence for a benefit is for weight loss, but even there the evidence supports only a modest short-term weight loss insufficient to positively affect cardiovascular risk factors or health conditions associated with being overweight or obese. Other possible benefits, such as enhanced athletic performance, enhanced energy, or a feeling of alertness, lack scientific support and/or they would provide only temporary benefits that are trivial in comparison to the risks of serious long-term or permanent consequences like heart attack, stroke, and death.

i. *Weight Loss.* As discussed above, the RAND report provides the most comprehensive review of efficacy studies for ephedrine alkaloid containing products. The RAND report found evidence that supported an association between short-term use of ephedrine, ephedrine plus caffeine, or dietary supplements that contain ephedrine alkaloids with or without herbs containing

caffeine, and a statistically significant increase in short-term weight loss compared to placebo. The RAND report concluded that products containing ephedrine alkaloids in combination with caffeine resulted in a modest weight loss of approximately two pounds per month more than placebo over a period of four to six months. RAND concluded that the use of ephedrine without caffeine was associated with a statistically significant increase in weight loss (1.3 pounds of weight loss per month) compared with that of placebo for up to four months of use. RAND identified a single trial of three months duration that assessed the effect of herbal ephedra versus placebo. Those in the ephedra arm lost 1.8 pounds more per month than did those in the placebo arm. We are unaware of any appropriate, well-designed studies showing an effect of dietary supplements containing ephedrine alkaloids on weight loss for more than six months. Such a long-term effect would be necessary to translate into health outcome improvements.

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

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

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

ii. *Enhancement of Athletic Performance.* The effects of synthetic ephedrine on athletic performance were assessed in seven studies that were reviewed in the RAND report. Despite the widespread marketing of products containing ephedrine alkaloids as performance-enhancers, the RAND report found no studies involving botanical ephedrine alkaloids, and very limited evidence involving synthetic ephedrine, to support the claims. Furthermore, the RAND report concluded that, "to show even a short-term effect of ephedrine, combination with caffeine was required." Therefore, there is no evidence to indicate that ephedrine alone enhances athletic performance. People who use dietary supplements containing ephedrine alkaloids for athletic performance are at risk for the same serious adverse events as individuals who use these products for other indications. As discussed above

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

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

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

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

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

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

A dietary supplement labeled for a very temporary, episodic use might not present an unreasonable risk if there were adequate evidence that the use resulted in a health benefit sufficient to outweigh the health risks. Any new indication would still be subject to our post-market risk evaluation as to whether it could be legally marketed. Conclusions regarding the benefit of dietary supplements containing ephedrine alkaloids for non-disease claims cannot be drawn solely from studies using synthetic ephedrine for specific

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

3. Conclusion

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

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

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

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

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

In addition, we considered other regulatory alternatives presented in the comments received.

A. Warning Statement Alone

We first proposed a warning statement in the June 4, 1997 proposed rule. At that time, we tentatively concluded that a warning statement was necessary to disclose material facts about the consequences of using these products, and that it would help to reduce the risk of an adverse event after use of dietary supplements containing ephedrine alkaloids. 62 FR at 30703. In our March 2003 **Federal Register** notice, we reopened the comment period to seek, among other things, comments on a revised warning statement that we were considering at that time for dietary supplements containing ephedrine alkaloids.

We received a number of comments on the proposed labeling requirements in the June 4, 1997 proposed rule and on the revised warning statement in our March 2003 **Federal Register** notice. Because we have decided to proceed under the adulteration provision in section 402(f)(1)(A) of the act rather than to require labeling for dietary supplements containing ephedrine alkaloids, these comments are moot to the extent that they discuss the substance or format of the warning statement. Nevertheless, comments regarding the sufficiency of a warning are relevant to this rulemaking.

(Comment 64) Many comments supported the use of a warning label as an effective way to protect public health, although they differed on the specific language and format of the warning. Many comments urged us to mandate strict warning labels to inform users about the potential health risks that have been reported to be associated with the use of dietary supplements containing ephedrine alkaloids. One comment stated that product labeling does influence

user behavior and strongly urged us to take action in the form of issuing a mandatory warning label for all dietary supplements containing ephedrine alkaloids. Several comments stated that there was a significant decrease in the number of AERs in certain states after their respective departments of health mandated label restrictions and strong cautionary statements. A number of comments stated that the warning labels voluntarily adopted and already used by industry are sufficient to protect the public from any risks. A number of comments proposed different labels to be adopted by the entire industry.

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

A few other comments asserted that warning labels are ineffective because serious adverse events have occurred after the initial use or after very short-term use of dietary supplements containing ephedrine alkaloids. As pointed out in the June 4, 1997 proposed rule, about 40 percent of the 600 AERs reported between 1993 and 1996 occurred with the first use or within one week of first use, providing little or no warning to consumers of risk. Many of the adverse events occurred in individuals who had no apparent risk factors, or who were unaware that they were at risk.

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

(Response) We agree that warning statements cannot adequately protect consumers from the risks associated with dietary supplements containing ephedrine alkaloids. Even if all consumers read the warnings and the warnings thoroughly describe the risks, many using these products may not be aware they have medical conditions or individual sensitivities that put them at greater risk for experiencing serious adverse effects. A full discussion of the risks to sensitive populations appears above in the response to comment 22.

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

dietary supplements containing ephedrine alkaloids would outweigh their known and reasonably likely risks when used episodically.

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

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

(Comment 65) Several comments compared sensitivity to ephedrine alkaloids in dietary supplements to sensitivity to food allergens. One comment

expressed the opinion that the number of individuals sensitive to ephedrine alkaloids in dietary supplements is either less than, or comparable with, those individuals who suffer from food allergies. One comment argued that warning statements are effective for people who know they are sensitive to a substance, such as peanuts. The comment suggested that if warning labels are considered sufficient in this context, they should also be considered sufficient in the context of dietary supplements containing ephedrine alkaloids. Another comment stated that, with respect to those individuals who are unaware that they may have one of the conditions that is contraindicated on the label, some misuse due to ignorance is unavoidable and occurs no matter what regulations are put in place.

(Response) We do not agree that individuals sensitive to ephedrine alkaloids in dietary supplements are comparable to individuals who suffer from food allergies. In the case of food allergies, individuals learn that they are allergic to certain foods (e.g., shellfish and nuts) and, because we require that the presence of the food ingredients be declared on the food label (see 21 CFR 101.4), these individuals can then avoid the problem ingredient by reading the food label. The physical manifestations of the allergic reaction are usually readily recognized by the consumer. In the case of the ephedrine alkaloids, as discussed above in the responses to comments 22 and 27, many individuals are not aware that they are sensitive to sympathomimetic agents, such as the ephedrine alkaloids, and may not recognize early signs of risk, such as elevated blood pressure or the adverse cardiovascular and nervous system effects related to the use of ephedrine alkaloids. In most instances, patients with nascent food allergies experience classic allergy symptoms, such as tingling lips, scratchy throat, wheezing, and shortness of breath, that alert

them to the development of a particular food allergy, whereas with ephedrine alkaloids, severe, life-threatening reactions, may occur at any time, even with the first exposure. Therefore, an ingredient declaration or a warning label statement cannot assist these consumers in adequately reducing their risk of adverse events.

B. Multiple restrictions

(Comment 66) Addressing the inadequacy of a warning statement alone, many comments supported multiple restrictions (e.g., dosage limits, ingredient combination restrictions, duration of use restrictions, label claim restrictions, GMP requirements, and warning label statements) to reduce the risk of adverse events. One comment pointed out that the frequency, severity, and the broad cross section of the population for which there are documented adverse events support at least this level of regulation. Some comments contended that we should establish more stringent regulations. Several of these comments recommended that we ban the use of ephedrine alkaloids in dietary supplements because of the serious health hazards associated with their use and the potential for abuse and misuse of these products.

(Response) We do not agree that the restrictions recommended in these comments will eliminate the risks imposed by dietary supplements containing ephedrine alkaloids. As discussed in the response to comment 26, we are not aware of any evidence that establishes a safe dose of ephedrine alkaloids in dietary supplements. Therefore, dose limitations cannot change the unfavorable risk-benefit ratio of these products. Similarly, a requirement for a label statement recommending that consumers limit the duration of product use will not provide adequate protection because adverse events sometimes occur after the first use or in the first few days. We also do not agree that

dietary ingredient restrictions, such as limiting the presence of other stimulant ingredients, will eliminate the unreasonable risk associated with the use of dietary supplements containing ephedrine alkaloids. As explained in section V.B.1 of this document, ephedrine alkaloids given alone can be expected to cause significant increases in blood pressure, although the presence of other stimulants combined with ephedrine alkaloids may increase the risks associated with use of these products. Finally, while GMP requirements may ensure consistent quality across dietary supplement products containing ephedrine alkaloids, the risks attributed to ephedrine alkaloids are due to their inherent pharmacological and physiological effects rather than the quality of their manufacture, although poor manufacturing could lead to additional risks, such as from the introduction of toxic impurities into the product.

C. Self-Regulation

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

(Response) We disagree with the comments that state that no FDA action is necessary because the industry will self-regulate. It is incumbent upon us to respond to the serious adverse events associated with the use of dietary supplements containing ephedrine alkaloids and other information about the risks of these products. We have been aware for several years that a number

of trade associations have policies concerning the formulation and labeling of dietary supplements containing ephedrine alkaloids. These voluntary industry standards are insufficient to alter the risk-benefit ratio for these products. Despite the fact that these industry standards are in place, we continue to receive reports of clinically significant adverse events following the consumption of dietary supplements containing ephedrine alkaloids. Some of these adverse events may be due to non-compliance with those voluntary standards; however, for the reasons stated in the response to comment 39, these types of standards, even if adhered to, would be insufficient to protect consumers from the risks posed by dietary supplements containing ephedrine alkaloids.

D. More Education

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

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

E. Nonbinding Guidance

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

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

F. Targeted Enforcement Actions

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

(Response) We find that individual enforcement actions against products containing high levels of ephedrine alkaloids are inadequate to protect the public health. Data from the scientific literature and AERs indicate that clinically significant adverse effects are not limited to the use of products containing high levels of ephedrine alkaloids (Ref. 109,134). Therefore, enforcement actions against products containing only high levels of ephedrine alkaloids would not be expected to eliminate the unreasonable risk presented by these products. We also note that rulemaking is a more efficient regulatory mechanism than individual enforcement actions in cases where hundreds of different products on the market contain the same ingredient that presents a risk to the public health, as is the case here. Without a regulation, we would be required to establish our case de novo with witnesses in every enforcement proceeding. Multiple proceedings would require multiple witnesses and extensive discovery, and would be extremely time-consuming and burdensome for both the courts and us. However, we point out that a regulation is not necessary to find that a dietary ingredient or a dietary supplement presents an unreasonable risk.

VII. Miscellaneous Issues

A. Freedom of Choice/FDA Bias

(Comment 71) Many comments stated that our attempt to regulate dietary supplements containing ephedrine alkaloids would erode personal freedom and the public's freedom of choice, values that the comments maintained were

established through the passage of DSHEA. Several comments stated that DSHEA gives the public a right to access affordable, natural and effective dietary supplements. A number of comments alleged that we issued the June 4, 1997 proposed rule because we are biased against dietary supplements. One industry comment accused us of selectively including information in the docket. Several of these comments alleged that our purpose for issuing the 1997 proposed rule was to protect the business interests of the pharmaceutical industry. Several comments explained that, if access to dietary supplements for weight loss is restricted, consumers will have little choice but to use prescription drugs. Many comments from consumers stated that use of prescription drugs for weight loss is both more costly and associated with more adverse effects than use of products containing natural herbs. Many of these comments stated that dietary supplements containing ephedrine alkaloids from natural sources are safe and have no side effects. Conversely, several comments stated that the perception that supplements are natural and, therefore, safe and acceptable alternatives to prescribed medications is erroneous and that there are serious concerns about the safety and efficacy of these products.

(Response) We deny these allegations of bias against the marketing and use of dietary supplements and any allegations of protecting or favoring the pharmaceutical industry. We support access to dietary supplements that are safe, properly labeled, and in compliance with federal law. However, we are also obligated under DSHEA to protect the public against dietary supplements that are unsafe or otherwise adulterated. Contrary to one comment's assertion, we did not base our decision on selectively chosen information; instead, we considered all information that was submitted to the relevant dockets, including more than 48,000 comments and hundreds of studies submitted by

the dietary supplement industry, trade associations, academics, health professionals, scientists, public health groups, and consumer groups. Given the scientific information about the pharmacology of ephedrine alkaloids, clinical studies examining their effects, and AERs, we found that there are serious and well-documented public health risks associated with the use of dietary supplements containing ephedrine alkaloids. Therefore, our obligation under DSHEA is to take action to address such risks, particularly in light of the products' lack of health benefits.

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

B. Conduct of the Advisory Committee Meetings

(Comment 72) Several comments stated that we conducted the October 1995 meeting of the Working Group and the 1996 meeting of the Food Advisory Committee in a manner that improperly influenced their deliberations and recommendations. These comments argued that we instructed the Committee members not to consider certain data (e.g., data concerning the use of ephedrine-containing OTC drug products for the treatment of asthma); misrepresented certain data (e.g., data concerning the AERs and data from clinical trials on the use of ephedrine in the treatment

of obesity); failed to present data that industry believed to be relevant to the evaluation (e.g., number of units of products sold during the period of time the AERs were received, data regarding whether a cause and effect relationship existed between dietary supplements containing ephedrine alkaloids and the adverse events reported to us); instructed the Committee to evaluate safety using an interpretation of "significant harm" (i.e., either a large number of adverse events or a serious adverse event in one individual) that is not specified in DSHEA; and improperly asked the Committee to recommend action to reduce the risks associated with the use of these products.

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

(Response) We disagree with the comments. The comments concerning the data and information we presented or did not present during the meetings are without merit because the essence of these comments is that they disagreed with our interpretation of the data or preliminary conclusions. Presenting our interpretation of the data and our preliminary conclusions is entirely appropriate and does not constitute undue influence over the Working Group or Food Advisory Committee (the Committees) (Ref. 137). Interested persons, including the dietary supplement industry, were provided with ample opportunity to express their views and present data they believed relevant to

the evaluation during the public hearing portions of the meetings or in written comments to the Committees. To the extent that specific comments on the data, our interpretation of the data, and our preliminary conclusions are relevant to this rulemaking, they are addressed in other sections of this document.

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

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

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

views and to question FDA officials about the available data, our interpretation of the data, and our tentative position.

Second, the Committees included consumer and industry representatives including two representatives from associations representing the dietary supplement industry. The consumer and industry representatives represented the views of consumers and industry throughout the meeting and made recommendations to us. All FDA-prepared materials to be considered by the Committees were sent to all members of the Committees, including the dietary supplement industry representatives, prior to the meeting.

Third, the Committees' meetings provided a forum for public discussion. Interested persons, including the dietary supplement industry, were provided with ample opportunity to express their views and present data they believed relevant to the evaluation during the public hearing portions of the meetings or in written comments to the Committees. During the Committees' meetings, we provided over two hours of public hearing time, which is twice the time required by our regulations, 21 C.F.R. ?14.29 (a).

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

VIII. Analysis of Impacts

A. Benefit-Cost Analysis

Introduction

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

assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). E.O. 12866 classifies a regulatory action as a significant regulatory action if it meets any one of a number of specified conditions, including having an annual effect on the economy of $100 million or more, adversely affecting a sector of the economy in a material way, adversely affecting competition, or adversely affecting jobs. E.O. 12866 also classifies a regulatory action as significant if it raises novel legal or policy issues. We have determined that this final rule is a significant regulatory action as defined by E.O. 12866 because the benefits of the rule could exceed $100 million per year and because the rule raises novel legal and policy issues.

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

Title II of the Unfunded Mandates Reform Act of 1995 (Public Law 104–4) requires cost-benefit and other analyses before any rule making if the rule

would include a "Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted annually for inflation) in any 1 year." The current inflation-adjusted statutory threshold is $113 million per year. We have estimated that the total cost of this final rule would be no more than $90 million per year. Therefore, we have determined that this final rule does not constitute a significant rule under the Unfunded Mandates Reform Act.

1. Regulatory Options

We discussed the following seven regulatory options in the benefit-cost analysis of the 1997 proposed rule: 1) take no action; 2) take no new regulatory action, but generate additional information on which to base a future regulatory action; 3) take the actions in the 1997 proposed rule; 4) take the proposed action, but with a higher potency limit; 5) remove dietary supplements that contain ephedrine alkaloids from the market; 6) take the proposed action, but do not require a warning statement; and 7) require a warning statement only (62 FR 30705). We later withdrew all elements of the proposed action except the warning statement and prohibition of dietary supplements that combine ephedrine alkaloids with other stimulants (65 FR 17474). In 2003, we issued a **Federal Register** notice seeking comment on, among other things, a revised warning statement consisting of a short warning on the principal display panel (PDP) and a more detailed warning elsewhere in the product labeling (68 FR 10417). We did not perform any economic evaluation of the revised warning statement at that time. We received additional comments on the revised warning statement. In addition, the comments on the 1997 proposed rule suggested some additional options. Considering the options from these sources, we address the following options in this analysis: 1) take no new regulatory

action; 2) remove dietary supplements containing ephedrine alkaloids from the market; 3) require the proposed warning statement, as revised in 2003; 4) require a warning statement, but modify it or require it only on certain products; and 5) generate additional information or take some action other than removing dietary supplements containing ephedrine alkaloids from the market or requiring warning statements. E.O. 12866 requires us to analyze regulatory options but recognizes that there are practical limits to the number of options that we can analyze. The options listed above encompass all or most of the significant suggestions raised in the comments.

2. Summary of Conclusions

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

3. Option One—Take No New Regulatory Action

We use this option as the baseline for determining the costs and benefits of the other options. Therefore, we do not associate costs or benefits with this option. Instead, we discuss the costs and benefits of taking no action in the context of the costs and benefits of the other options. As we discuss more fully under the other options, the expected number of adverse events from these products will probably decline, over time, even if we take no regulatory action, for two reasons. First, many firms are moving away from the use of ephedrine alkaloids because of media coverage of adverse events associated with these

products, the high cost of liability insurance, and the potential for legal actions by consumers. Second, some State and local governments have either banned the sale of these products or placed various requirements or restrictions on sales of these products.

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

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

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

from dietary supplements, and we do not know the associated dose-response function. Therefore, the best available approach, and the method we apply here, is to use AERs to generate estimates of the number of adverse events associated with dietary supplements containing ephedrine alkaloids.

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

Use of AERs in Estimating Benefits and Baseline Number of AERs

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

(Comment 73) A number of comments on the 1997 proposed rule addressed the issue of the baseline number of AERs. Some comments objected to adjusting the number of AERs with assumptions designed to reflect uncertainty over the relevance of those AERs. One comment said we should have used only those AERs that we were certain had been caused by dietary supplements containing ephedrine alkaloids. Other comments simply pointed out that some adverse events might not have been caused by dietary supplements containing ephedrine alkaloids.

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

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

A number of comments discussed adverse events that purportedly would have occurred without consumption of dietary supplements containing

ephedrine alkaloids. These comments argued that we probably generated a large number of irrelevant AERs by asking consumers to report ubiquitous symptoms as adverse events that may have been caused by these products.

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

Other comments addressed one or more of the other articles that we listed in the 2003 reopening of the comment period. Many comments criticized one or more of those studies on various bases. Other comments supported one or more of those studies. One comment argued that we presented a biased list of studies because we ignored four other articles that were published at about

the same time as the articles that we listed. Some comments noted that RAND said that clinical trials that they reviewed had enrolled enough patients to detect serious adverse events at rates of 1 per 1,000 or higher.

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

(Response) Although uncertainty remains over the exact number of adverse events that are caused by dietary supplements containing ephedrine alkaloids, we disagree that, when estimating the number of adverse events, we should use only those AERs that we or others have proven to have been caused by dietary supplements containing ephedrine alkaloids. The comments appear to suggest that we should adopt a standard of absolute proof that a dietary supplement caused an individual adverse event. However, establishing absolute proof for individual cases is very difficult for dietary supplements or most other substances other than direct poisons. It is appropriate in the case of dietary supplements containing ephedrine alkaloids to estimate the number of adverse events prevented by this rule based upon scientifically established pharmacological effects of ephedrine alkaloids and the clinical and epidemiological evidence. The RAND report used the term "sentinel events" to describe adverse events that involved ephedrine alkaloids and for which RAND could exclude alternative explanations for the event with "reasonable

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

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

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

caused by these products. Although not as rigorous as an epidemiological case control study, this evidence is the best available to estimate the benefits of this rule.

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

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

We did not attempt to forecast trends in the number of adverse events in the analysis of the proposed rule, and we have not done so in this analysis. Forecasting trends in the number of adverse events would be difficult, and any such forecasts would be associated with large uncertainty ranges. Although we recognize that some firms may have recently discontinued the use of

ephedrine alkaloids in some or all of their products, we have insufficient information to revise the results of the RAND report on that basis.

Assumptions used in analysis of the final rule:

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

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

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

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

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

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

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

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

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

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

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

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

(Response) In order to express the continuing uncertainty over the reporting rate, we have calculated benefits based on reporting rates of 10 percent, 50 percent, and 100 percent of sentinel and possible sentinel events. Although the reporting rate could be lower than 10 percent, the severity of the adverse events under consideration and the level of media coverage suggest that the reporting rate may be 10 percent or higher. The assumed 100 percent reporting rate generates a lower bound number of adverse events. We selected 50 percent as an intermediate number. We used a 10 percent reporting rate in our summary statements to simplify the presentation of the results and because 10 percent reporting appears to be a reasonable point estimate, taking into account the seriousness and media coverage of these adverse events and the estimated reporting rates of 1 percent or lower for adverse events involving drugs (Ref. 32,139). The 10 percent reporting rate applies to serious events only, and incorporates the fact that a report of a serious adverse event had to fulfill the RAND criteria in order to be included as a sentinel or possible sentinel event. We did not consider non-sentinel events in the analysis, as explained below.

Valuing reductions in adverse events

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

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

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

any reduction in life expectancy due to the MI. For this rule, we based the years of disability or pain and suffering on the ages of those suffering non-fatal myocardial infarction in the RAND report (Ref. 141). RAND reported summary information on age by type of adverse event using three age categories (13 to 30, 31 to 50, and 51 to 70). We took the midpoints of the three age categories and constructed a weighted average based on the proportion of people suffering that adverse event in those categories. We then compared that age to an average life expectancy in the United States in 2001 of 77.2 years to determine the years of disability or pain and suffering or both (Ref. 142).

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

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

(Response) As we indicated previously, we have revised our estimate of the number of relevant AERs to reflect the RAND report. The definition that RAND used for sentinel events involved investigating alternative explanations

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

Serious vs. minor adverse events

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

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

Risks of Substitutes and Weight Regain

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

Some comments discussed what would happen if consumers stopped using dietary supplements containing ephedrine alkaloids and did not switch to equally effective alternative weight loss methods. Some comments discussed the extent and rising trend of obesity in the United States. Some comments noted that obesity increases the risk for heart attack, stroke, diabetes, and cancer. However, other comments argued that any countervailing health costs that would result if people stopped using dietary supplements containing ephedrine alkaloids to lose weight would be small or nonexistent. Some comments suggested there were no clear health benefits from the amount of weight loss that the RAND report attributed to dietary supplements containing ephedrine alkaloids. Other comments disagreed and argued that there were clear health benefits from the amount of weight loss that the RAND report attributed to dietary supplements containing ephedrine alkaloids. One comment argued that, although people often regain weight that they lose during a diet program, people who have participated in diet programs nevertheless generally maintain lower weights than those who have not.

(Response) Subtracting the value of countervailing health effects posed by substitute products and activities from the value of the health benefits from removing dietary supplements containing ephedrine alkaloids from the market to obtain the net health benefits is consistent with our approach for estimating benefits. (For purposes of this economic impact analysis, "health benefits"

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

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

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

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

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

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

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

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

Risks of Certain Dietary Supplements Containing Ephedrine Alkaloids from the Market

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

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

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

(Response) The RAND report found little scientific agreement on the dose-response relationship for ephedrine alkaloids (Ref. 21,22). Therefore, we are unable to estimate the impact of exempting products from this rule based on the level of ephedrine alkaloids that they contain. As we discussed earlier in the preamble, we have determined that botanical sources of ephedrine alkaloids in traditional Asian herbal therapies are not covered by this rule. We do not have sufficient information to estimate the impact of exempting products based on the other considerations suggested in the comments, including type of product, label warnings, or directions for use.

b. *Revised Benefit Estimates*Based on the preceding discussion, we have revised our estimate of the benefits of removing dietary supplements containing ephedrine alkaloids from the market. The social benefits of removing dietary supplements containing ephedrine alkaloids from the market consist of the increase in consumer utility that would be generated by any net health benefits resulting from removing dietary supplements containing

ephedrine alkaloids from the market. The following table provides an estimate of the number of the various types of serious adverse events that we might eliminate by removing dietary supplements containing ephedrine alkaloids from the market, along with an estimate of the utility loss prevented by that reduction. As we discussed above, benefits could be much lower and potentially zero if the health risks posed by substitute weight loss or sports performance products, such as other dietary supplements containing sources of sympathomimetics, were comparable to the health risks posed by ephedrine alkaloids.

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

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

Type	Annual Number Prevented	QALY Loss Per Case	Medical Costs per Case
Death	0.7 to 1.2	NA (used VSL)	$25,742
MI (heart attack)	0.6 to 1.0	0.29	$30,586

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

Type	Annual Number Prevented	QALY Loss Per Case	Medical Costs per Case
CVA (stroke)	1.5 to 2.1	0.2	$20,898
Other Cardiovascular (e.g. Cardiomyopathy, Ventricular Tachycardia)	0.1 to 0.2	0.29	$30,586
Other Neurological (e.g. Transient Ischemic Attack)	0.1	minimal	$13,212
Seizure	0.5 to 0.9	minimal	$11,812
Psychiatric	0.9 to 1.3	minimal	$6,927

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

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

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

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

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