DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 111

[Docket No. 95N–0304]

RIN 0901–AA59

Dietary Supplements Containing Ephedrine Alkaloids

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to make a finding, which will have the force and effect of law, that a dietary supplement is adulterated if it contains 8 milligrams (mg) or more of ephedrine alkaloids per serving, or if its labeling suggests or recommends conditions of use that would result in intake of 8 mg or more in a 6-hour period or a total daily intake of 24 mg or more of ephedrine alkaloids; require that the label of dietary supplements that contain ephedrine alkaloids state ''Do not use this product for more than 7 days''; prohibit the use of ephedrine alkaloids with ingredients, or with ingredients that contain substances, that have a known stimulant effect (e.g., sources of caffeine or yohimbine), which may interact with ephedrine alkaloids; prohibit labeling claims that require long-term intake to achieve the purported effect (e.g., weight loss and body building); require a statement in conjunction with claims that encourage short-term excessive intake to enhance the purported effect (e.g., energy) that ''Taking more than the recommended serving may result in heart attack, stroke, seizure or death''; and require specific warning statements to appear on product labels. FDA is proposing these actions in response to serious illnesses and injuries, including multiple deaths, associated with the use of dietary supplement products that contain ephedrine alkaloids and the agency's investigations and analyses of these illnesses and injuries. FDA is also incorporating by reference its Laboratory Information Bulletin (LIB) No. 4053, that FDA will use in determining the level of ephedrine alkaloids in a dietary supplement.

DATES: Written comments by August 18, 1997. The agency proposes that any final rule that may issue based on this proposal become effective 180 days after date of publication of the final rule.

ADDRESSES: Submit written requests for single copies of the analytical method LIB No. 4053 to the Director, Office of Constituent Operations, Industry Activities Staff (HFS–565), Food and Drug Administration, 200 C St. SW., rm. 5827, Washington, DC 20204. Send two self-addressed adhesive labels to assist that office in processing your requests. Submit written comments to the Dockets Management Branch (HFA–305), Food and Drug Administration, 12410 Parklawn Dr., rm. 1–23, Rockville, MD 20857. Requests and comments should be identified with the docket number found in brackets in the heading of this document. A copy of the analytical method LIB No. 4053, redacted adverse event reports (AER's) associated with the use of dietary supplements containing ephedrine alkaloids as well as copies of any accompanying medical records, and received comments are available for public examination in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

FOR FURTHER INFORMATION CONTACT: Margaret C. Binzer, Center for Food Safety and Applied Nutrition (HFS–456), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, 202–401–9859, FAX 202–260–8957, or E-mail M2B@FDACF.SSW.DHHS.GOV.

SUPPLEMENTARY INFORMATION:

I. Background

A. Characteristics of Ephedrine Alkaloids

Dietary supplements containing ephedrine alkaloids are widely sold in the United States (Refs. 1 through 3). The ingredient sources of the ephedrine alkaloids include raw botanicals and extracts from botanical sources. Ma huang, *Ephedra,* Chinese *Ephedra,* and epitonin are several names used for botanical products, primarily from *Ephedra sinica* Stapf, *E. equistestina* Bunge, *E. intermedia* var. *tibetica* Stapf and *E. distachya* L. (the *Ephedras*), that are sources of ephedrine alkaloids. These alkaloids, ephedrine, pseudoephedrine, norpseudoephedrine, norephedrine, methylephedrine, methylpseudoephedrine, and related alkaloids, are naturally occurring chemical stimulants (Refs. 4 through 8). Although the proportions of the various ephedrine alkaloids in botanical species vary from one species to another, in most species used commercially, ephedrine is the most predominant alkaloid.

The ephedrine and related alkaloids are amphetamine-like compounds. They exhibit some common types of effects but vary in the relative intensity of these effects (Table 1) (Refs. 5, 6, and 9 through 15). For example, ephedrine is a cardiovascular system (CVS) and nervous system (NS) stimulant. Pseudoephedrine has some CVS and NS stimulatory effects but is less potent than ephedrine. Norephedrine (also called phenylpropanolamine) is similar to ephedrine in its NS stimulant effects but has fewer CVS stimulant effects than ephedrine (Refs. 12 and 16 through 18). Although norephedrine is often a minor ephedrine alkaloid constituent, in humans it can be produced from ingested ephedrine through normal metabolic processes (Refs. 9, 19, and 20). Thus, its presence in body tissues and fluids may be detected, and its physiological effects can occur, even if norephedrine is not contained in meaningful amounts in the original supplement product. Data on the other ephedrine alkaloids and related alkaloids are limited, and thus their physiological and pharmacological effects are largely unknown (Ref. 15).

TABLE 1.—PATTERNS OF SIGNS AND SYMPTOMS ASSOCIATED WITH DIETARY SUPPLEMENTS CONTAINING EPHEDRINE ALKALOIDS

Organ/system involved	Clinical significance	Signs and symptoms
Cardiovascular system	Serious	Dysrhythmias, severe hypertension, cardiac arrest, angina, myocardial infarction, and stroke [1]
	Less clinically significant	Tachycardia, mild hypertension, palpitations.
Nervous system	Serious	Psychosis, suicidal, altered or loss of consciousness (including disorientation or confusion), and seizures.
	Less clinically significant	Anxiety, nervousness, tremor, hyperactivity, insomnia, altered behavior, memory changes.
Gastrointestinal (GI)	Serious	Altered serum enzymes, hepatitis.
	Less clinically significant	GI distress (nausea, vomiting, diarrhea, constipation).

TABLE 1.—PATTERNS OF SIGNS AND SYMPTOMS ASSOCIATED WITH DIETARY SUPPLEMENTS CONTAINING EPHEDRINE ALKALOIDS—Continued

Organ/system involved	Clinical significance	Signs and symptoms
Dermatologic	Serious	Exfoliative dermatitis.
	Less clinically significant	Nonspecific rashes.
General manifestations		Numbness, tingling, dizziness, fatigue, lethargy, weakness.

[1] For the purposes of this document, strokes (i.e., cerebrovascular accidents) are considered to be related to the cardiovascular system, because predisposing or inciting factors include hypertension, dysrhythmias and ischemia, although it is recognized that the consequences affect the central nervous system.

B. The Availability of Ephedrine Alkaloids

To determine the types of ephedrine alkaloid-containing dietary supplements available in the marketplace, the agency has collected over 125 dietary supplement products labeled as containing a known source of ephedrine alkaloids during the past 2 years (Refs. 1 and 2). These products show that ephedrine alkaloid-containing-dietary supplements are marketed in a variety of forms, including capsules, tablets, powders, and liquids. The source of the ephedrine alkaloids in these supplements vary from the raw botanical to powdered plant material and concentrated extracts; however, most of the products contain concentrated extracts. Although FDA is aware that some companies have changed their labeling and formulation since the market review, this review of the marketplace reflects the general contours of products currently sold in the United States.

Ephedrine alkaloids are present in some products as a single ingredient, but more commonly, they are combined with other ingredients, including vitamins, minerals, amino acids, and other botanicals (Refs. 1, 2, and 21). Most of the dietary supplements that contain an ingredient source of the ephedrine alkaloids also contain between 6 and 20 other ingredients. Some of these other ingredients have known or suspected physiological and pharmacological activities that have the potential for interacting with the ephedrine alkaloids so as to increase their effects. For example, the majority of dietary supplements containing ephedrine alkaloids also contain a source of xanthine alkaloids (e.g., caffeine), another stimulant substance that is known to increase the effects of ephedrine alkaloids (Refs. 7, 16, 22, and 23).

Because product labels do not usually provide information on product composition (Ref. 24), and there are no data bases containing such data, FDA laboratories analyzed the products collected to quantify the levels of ephedrine alkaloids (Refs. 1, 2, 21, and 25). Results of the analyses show that these products, taking into account the labeled recommended serving instructions, are likely to provide intakes of ephedrine alkaloids that range from below the detectible limits of FDA's analytical method to 110 mg per serving (i.e., per single use) (Refs. 1, 2, 21, 25, and 26). Most of the products, regardless of their promoted use, had ephedrine alkaloid levels at or above 10 mg per serving.

Many of the dietary supplement products that FDA collected were promoted for uses such as weight loss, body building, increased energy, increased mental concentration, increased sexual sensations, or euphoria or as alternatives to illicit street drugs (Refs. 1, 2, and 25). The majority of the products collected also bore warning statements on their labels (Refs. 1, 2, and 27). The warning statements varied from general precautions, suggesting that the consumer check with a health care professional before beginning any diet or exercise program, to more specific warning statements. The more specific warning statements contained several elements, including cautions that the consumer 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 (Refs. 1, 2, 25, and 27).

C. Adverse Events Associated With Ephedrine Alkaloids

Since 1993, FDA has received more than 800 reports of illnesses and injuries (AER's) associated with the use of more than 100 different dietary supplement products that contained, or were suspected to contain, ephedrine alkaloids. These adverse events tended to involve CVS effects and NS effects. FDA evaluated the AER's showing CVS and NS effects and found that the single most common element was that the products contained, or were thought to contain, a source of ephedrine alkaloids. Approximately 50 to 60 percent of the AER's associated with use of dietary supplements were for such products.

The AER's associated with the ephedrine alkaloid-containing products included consistent patterns of signs and symptoms among both otherwise healthy individuals and those with underlying diseases or conditions. These signs and symptoms included rapid and irregular heart rhythms, increased blood pressure, chest pain, anxiety, nervousness, tremor, hyperactivity, and insomnia (i.e., inability or difficulty in sleeping) and were associated with clinically significant conditions, including heart attack, stroke, psychoses, seizure, and, in a few cases, death. Many of these signs and symptoms occurred in young adults who generally would not have been expected to be at high risk for such conditions (e.g., heart attack and stroke). Many adverse events were reported to occur with the first use or within the first 2 weeks of use. Although the majority occurred in women, men also reported experiencing adverse events.

The nature and patterns of these AER's are consistent with the known physiological and pharmacological effects of ephedrine alkaloids as described in: (1) Pharmacology texts for single ephedrine alkaloid products, (2) case reports of adverse effects from the scientific literature related to the pharmaceutical use of ephedrine alkaloids, (3) adverse events reported in controlled clinical trials using ephedrine in the treatment of obesity, and (4) known safety concerns with traditional medical uses of botanicals that contain ephedrine alkaloids. As a result, FDA focused its investigation on ephedrine alkaloids as a likely factor in the rapidly increasing number of serious AER's associated with the use of dietary supplement products.

D. Review Activities

The growing number and consistency of reports of serious adverse events associated with a wide variety of ephedrine alkaloid-containing dietary supplements, and the virtual absence of publicly available safety data on these supplements, prompted FDA to convene an ad hoc Working Group of its Food

Advisory Committee (the Working Group) (Refs. 27 through 29).

1. The Food Advisory Committee Working Group Meeting on Dietary Supplements Containing Ephedrine Alkaloids

On October 11 and 12, 1995, the Working Group, which consisted of medical and other scientific experts from outside FDA as well as industry and consumer representatives, considered the potential public health problems associated with the use of dietary supplements and other food products containing ephedrine alkaloids.

The Working Group reviewed the evidence on the occurrence of adverse events associated with the use of ephedrine alkaloids. This evidence included the known pharmacology of ephedrine alkaloids, numerous case reports published in the scientific literature, and published findings from clinical studies investigating the use of ephedrine in the treatment of obesity (Ref. 30). The evidence also included over 325 AER's that had been received by FDA that were associated with the consumption of dietary supplements known to contain, or suspected of containing, ephedrine alkaloids (Refs. 29 and 31). The Working Group also considered public comments made during the meeting (Ref. 27).

Following their review of this evidence, the members of the Working Group agreed that the use of certain dietary supplements containing ephedrine alkaloids may cause consumers to experience serious adverse events. On this basis, the Working Group recommended that FDA: (1) Establish single serving and daily total use limits for ephedrine and total ephedrine alkaloids; (2) require warning or cautionary statements on the labels of these products; and (3) establish good manufacturing practice (GMP) requirements, including proper botanical identification and standardization of the ephedrine alkaloid and ephedrine content in concentrated extracts. Several members of the Working Group suggested that ephedrine alkaloids be limited to 25 mg per single serving and 100 mg total daily use. Other members suggested a variety of lower levels of ephedrine alkaloids per serving. The Working Group also discussed specific warning label statements but failed to agree on the wording of the warning statements.

2. The Food Advisory Committee Meeting

In the 6 months that followed the Working Group meeting, the number of reports of adverse events associated with the use of dietary supplements thought to contain ephedrine alkaloids doubled. In addition, FDA received information on two deaths of young adult males in which the medical examiners specifically attributed the cause of death to use of ephedrine alkaloid-containing dietary supplements (see medical examiners' reports in Adverse Reaction Monitoring System (ARMS) No. 10862 and 11134). FDA analyzed samples of products that consumers claimed that they had consumed and suffered an adverse event and found that the ephedrine alkaloid levels in many of these products were below the 25-mg limit suggested by certain members of the Working Group.

In light of the rapidly increasing numbers of adverse events as well as of the new analytical information on AER-related intakes of ephedrine alkaloids, FDA recognized that a determination on how to deal with dietary supplements that contained these substances could not be further delayed. Thus, FDA convened its Food Advisory Committee in conjunction with the Working Group to review and provide final recommendations on what to do with ephedrine alkaloid-containing dietary supplements.

The Food Advisory Committee met on August 27 and 28, 1996. The meeting included all members from the Working Group who were available to attend the meeting, as well as additional experts to replace those experts unable to attend or to fill out the range of expertise needed to appropriately evaluate the subject. FDA asked the Food Advisory Committee to consider the safety of using dietary supplements containing ephedrine alkaloids and to make specific recommendations on how to resolve the public health concerns surrounding their use (Ref. 25). The Food Advisory Committee reviewed the evidence that had been presented to the Working Group as well as new data and information that had become available since the October 1995 Working Group meeting.

Following a review of the totality of the available evidence, the October 1995 recommendations of the Working Group, public comments, and considerable discussion, the Food Advisory Committee agreed that FDA should take action to address the rapidly evolving and serious public health concerns associated with the use of ephedrine alkaloid-containing dietary supplements (Ref. 25). The Food Advisory Committee could not, however, come to consensus on a specific approach to the public health concerns. Over half of the Food Advisory Committee members stated that, based on the available data, no safe level of ephedrine alkaloids could be identified for use in dietary supplements (Ref. 25). Many of these members expressed concern that many individuals who would be at risk if they were to use products were unaware of that risk because many of the conditions that increase the risk of adverse events may not be self-evident (Ref. 25). Consequently, they recommended removing dietary supplements containing ephedrine alkaloids from the market (Ref. 25). Other members of the Food Advisory Committee suggested that the agency establish conditions of use that would reduce the risk of adverse events, including establishing ''reasonably'' safe per serving and daily use levels for both ephedrine alkaloids and ephedrine as well as other requirements (Ref. 25).

II. FDA's Response

Following the August 1996 meeting of the Food Advisory Committee, the agency completed its review of the majority of the AER's associated with these products and reviewed the discussions and the recommendations of the Food Advisory Committee, the scientific literature, the views expressed in public comments, and other data. Based on this information, the agency has tentatively concluded that use of ephedrine alkaloids raises important public health concerns, that the risks these substances create are potentially very serious, and that action must be taken to protect the public health.

A. Summary of Initial Considerations

Between 1993 and 1996, FDA received a rapidly escalating number of AER's associated with the use of dietary supplements, some that contained ephedrine alkaloids, some that did not (Refs. 32 through 34). Figure 1 shows that in the 3 years since the initiation of an adverse event monitoring system for special nutritional products, the number of AER's received by the agency on dietary supplements has quadrupled.

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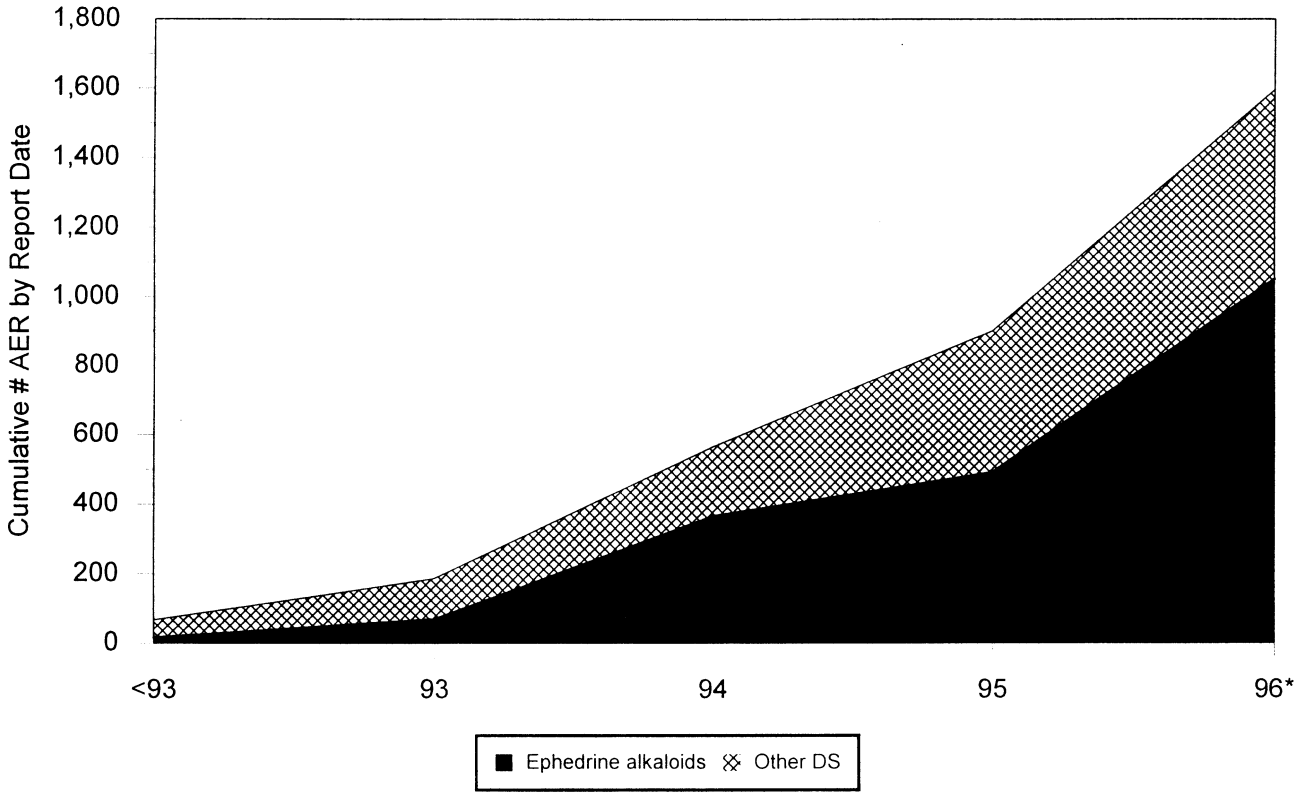
Figure 1: Time Trends in Adverse Events Associated with Dietary Supplements



* 1996 estimated from data as available 08/26/96 (DS=461, ephedrine = 371)

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Many of these reports have been for clinically significant events (e.g., heart attack, stroke, seizures) that were observed most often in young adults for whom the risk of these types of events are generally low (see Figure 2, which summarizes data from the AER's relative to the age and gender of individuals experiencing an adverse event). When FDA examined the products reported to be associated with the CVS and NS effects, the most common element among them was that they involved products that contained or were believed to contain an ingredient source of ephedrine alkaloids. Thus, FDA focused its investigation on the ephedrine alkaloids in dietary supplement products.

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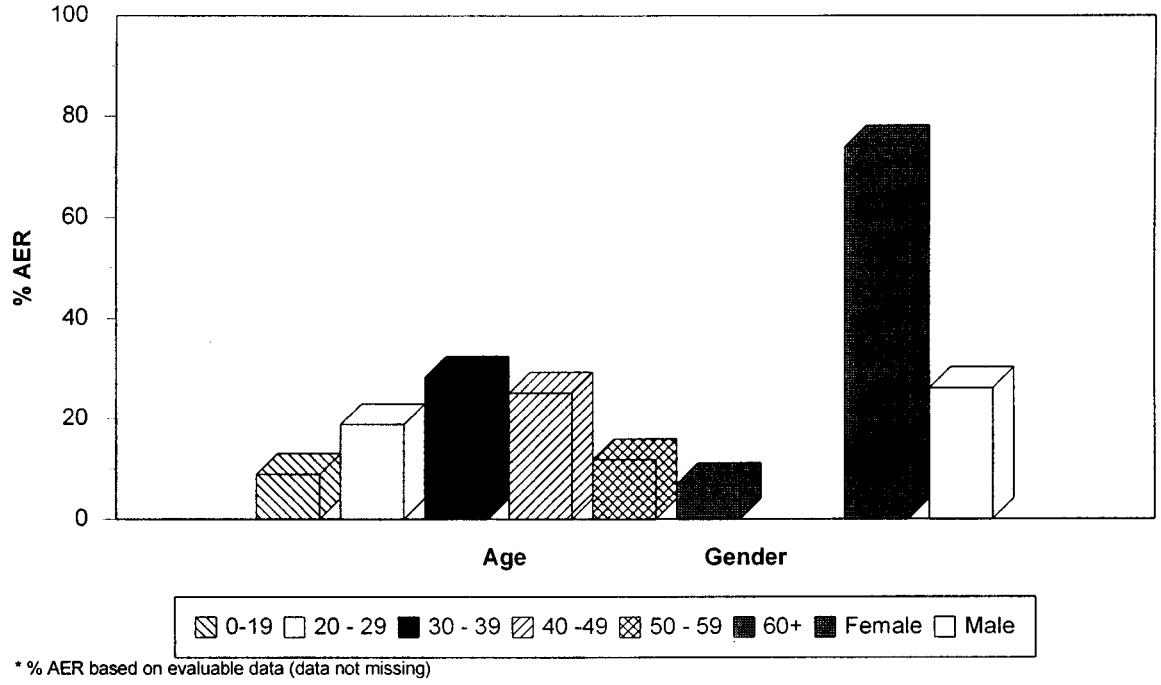
Figure 2: Age and Gender Associated with Adverse Events



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However, many of the ephedrine alkaloid-containing products also contained other ingredients (e.g., amino acids, vitamins and minerals, other botanicals) whose possible influence on the observed AER's could not be ignored. Upon examination of the types of other ingredients, FDA tentatively concluded that these other ingredients should not be the primary focus of its evaluation because these ingredients, unlike the ephedrine alkaloids, did not have a history (in the amounts likely to be found in dietary supplements) of being able to produce the types of serious adverse events being observed. For example, many ephedrine alkaloid-containing dietary supplements also contain known stimulants (e.g., sources of caffeine). While caffeine is known to stimulate the NS, in the amounts likely to be found in dietary supplements it is not expected to produce effects such as stroke, heart attack, and seizure. Nonetheless, FDA remained aware of the possibility that other ingredients in these dietary supplement products contributed to the adverse events reported. For example, other stimulants in the ephedrine-containing dietary supplements could enhance the known stimulant effects of ephedrine alkaloids. Likewise, substances that affect kidney function (e.g., sources of salicin, concentrated amino acids) could influence the body's ability to ''clear'' or rid itself of ingested ephedrine alkaloids.

The agency also considered in its evaluation the fact that botanical sources contain mixtures of ephedrine alkaloids that may have slightly different effects (e.g., additive or interactive effects) than those from a single ephedrine alkaloid, as found in over-the-counter (OTC) products. The agency compared the observed effects of supplement products with the known physiological and pharmacological effects of single sources of the alkaloids that are used as ingredients in several drugs (e.g., ephedrine in OTC bronchodilator products, pseudoephedrine in cough and cold preparations, and phenylpropanolamine in anoretic products). However, the agency was not able to find definitive evidence to evaluate whether ephedrine alkaloids from botanical sources are metabolized differently than those from pharmaceutical sources, and in the absence of more directly relevant data for dietary supplement products, the agency considered it appropriate to rely on evidence from pharmaceutical sources of single ephedrine alkaloids in assessing the effects of botanical sources (see section II.C.2. of this document).

B. FDA's Strategy for Evaluation

FDA considered five questions in evaluating the reports of adverse events involving ephedrine alkaloids that it

had received. These questions were designed to help the agency discern relationships among AER's where direct and readily interpretable clinical studies were not available, and where multiple host or product factors may have affected any association (Refs. 35 through 37). The questions focused the evaluation on whether there was a likely association between the ephedrine alkaloids and the adverse events that had been reported and on the strength, nature, and biological plausibility of any association. These questions were:

(1) Using the AER's on marketed ephedrine alkaloid-containing dietary supplements from FDA's passive surveillance system, are there consistent patterns of signs and symptoms associated with the use of a number of different ephedrine alkaloid-containing dietary supplement products?

(2) Are the patterns of the signs and symptoms consistent with the available scientific evidence and known physiologic and pharmacologic effects of ephedrine alkaloids?

(3) Is there sufficient evidence that the relationships are temporally correct, that is, does exposure occur temporally before the onset of the observed patterns of signs and symptoms?

(4) Is there other evidence of causality, even in the absence of controlled trials, e.g., evidence of dechallenge (improvement or resolution of the signs and symptoms when use of the product is discontinued) or positive rechallenge (reoccurrence of the signs and symptoms when reexposed to ephedrine alkaloids)?

(5) Considering the totality of the available information, is there a biologically plausible explanation for the adverse events?

Finally, in fully evaluating the public health concerns associated with these products, the agency evaluated the potential impact of other factors that could influence final decisions on the best approach to addressing the public health concerns.

C. Evaluation and Tentative Conclusions of the Agency

1. Using the AER's From FDA's Passive Surveillance System for Dietary Supplements, FDA Has Tentatively Concluded That There Are Consistent Patterns of Signs and Symptoms Associated With the Use of a Number of Different Ephedrine Alkaloid-Containing Dietary Supplement Products

In preparation for its August 27 and 28, 1996, Food Advisory Meeting, FDA reviewed each of the approximately 600 AER's that it had received before June 7, 1996 (Refs. 31 and 38). The adverse events associated with ephedrine alkaloid-containing dietary supplement products ranged from those with clinically serious sequelae (such as abnormal heart rhythms, chest pain, heart attack, stroke, significant elevations in blood pressure, seizure, hepatitis, coma, psychosis, and death) to those with less clinically significant signs and symptoms (such as nervousness, dizziness, tremor, minor alterations in blood pressure or heart rate, headache, and gastrointestinal distress) (see Table 1). Although many of the AER's crossed clinical categories, approximately 15 percent of the reports described serious cardiovascular effects, including abnormal heart rhythms, stroke, heart attack, and cardiomyopathy (disease of the heart muscle). Approximately 16 percent of the reports mentioned serious NS effects, including seizure, psychosis, mania, severe depression, vestibular (inner ear) disturbances, and loss of consciousness. Other clinically serious or potentially serious adverse effects reported to be associated with the use of these products included elevations of liver function tests or overt hepatitis (4 percent), myopathies (disease of muscle, particularly skeletal muscle) (3 percent), disturbances of the genitourinary system (e.g., urinary retention, urinary infection, prostatitis (inflammation of the prostate gland), and epididymitis (inflammation of the epididymis, part of the male genitourinary tract)) (3 percent), and dermatologic manifestations (including systemic rashes which appear to be immune mediated or allergic in nature) (6 percent). Approximately 30 percent of the reports mentioned other effects, including gastrointestinal distress, abnormal blood sugar levels or diabetes, blood disorders (including increased bleeding tendencies and abnormal blood cell counts), thyroid disorders, and addiction to the product. Finally, approximately 60 percent of the adverse events were characterized by general stimulant effects on the CVS and NS of a ''less clinically serious'' nature, including anxiety, nervousness, hyperactivity, tremor, insomnia, and altered heart rate or rhythms. However, FDA recognized that these reports of less clinically significant effects could be indicative of early warnings of serious cardiovascular or nervous system risks if product use were to continue.

Serious adverse events were reported for a number of different products promoted for a variety of uses and marketed in a variety of formulations (Refs. 27, 31, and 38). Of these, where there was sufficient information to evaluate how the product was marketed or used, approximately 92 percent of the adverse events were related to the use of products marketed for weight loss and energy purposes, and 5 percent were related to products promoted for enhancing athletic performance or body building, although there was overlap among these uses. Approximately 2 percent of the adverse events were related to products marketed as alternatives to illicit street drugs or for euphoric purposes. (This distribution of types of products parallels the observations made from FDA's market review, which found that most of the dietary supplements containing ephedrine alkaloids bear weight loss and energy claims on their labels or in their labeling (Refs. 1 and 2).) Moreover, specific types of adverse events did not appear to be limited to products promoted for any single use, such as weight loss, energy, or euphoria.

The adverse events were reported to occur in both healthy individuals and in individuals with underlying diseases or conditions that may have influenced the frequency, pattern, or severity of the adverse event (Refs. 25, 27, 31, and 38). Of great concern to the agency are the heart attacks, strokes, seizures, and other clinically serious illnesses and injuries reported to occur in young adults (Figure 2). In approximately 56 percent of the reported adverse events, the injured party was less than 40 years of age, and approximately 25 percent of injuries occurred in those between 40 and 49 years of age. Generally, significant CVS or NS risk factors are not expected in these age groups. Almost 75 percent of the adverse events were reported to occur in females, often using products promoted for weight loss. The higher frequency of adverse events in women most likely reflects a difference in product use (i.e., women predominantly use products marketed for weight loss and energy purposes). However, gender predominance in these ratios may also occur because of gender-related differences in metabolism of ephedrine alkaloids, or gender-related differences in the numbers and types of tissue receptors interacting with ephedrine alkaloids (Refs. 39 through 41).

Data on duration of use of ephedrine alkaloid-containing dietary supplements relative to the occurrence of AER's can also be used to examine the similarity of patterns of adverse events across different types of exposures and individual sensitivities. Figure 3 summarizes the duration of use data collected from the AER's associated

with products containing ephedrine alkaloids. As shown in Figure 3, this information reveals that about 59 percent of the adverse events were reported to occur within 4 weeks of starting to use the product. About 14 percent of the reported adverse events occurred on the first day of using the dietary supplement (Ref. 38) (see ARMS No. 10009 and 11619 in the Appendix to this document) and, in a few cases, on the initial use (Ref. 38) (ARMS No. 11401 in the Appendix to this document). Of equal concern to the agency are reports of serious adverse events occurring within a relatively short time period after consumers began to use the products or consumers began to start using the products after having stopped use for a period of time (ARMS No. 11076 in the Appendix to this document).

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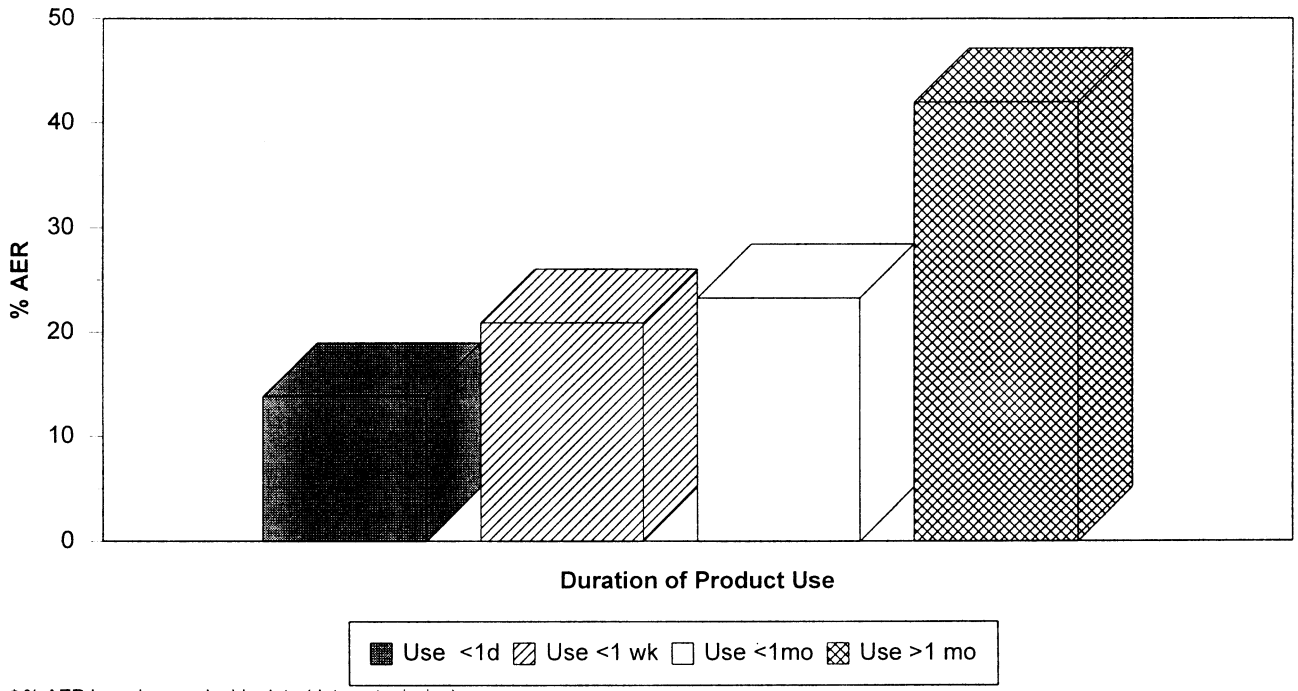
Figure 3: Durations of Product Use Associated with Adverse Events



* % AER based on evaluable data (data not missing)

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Adverse events appear to reflect different inherent types of individual sensitivities relative to dose levels, frequency or duration of use, and subsequent results of sympathomimetic stimulation. In some cases, particular events appear to occur as the result of increased individual susceptibility to the effects of sympathetic stimulation (Refs. 39 through 42). For example, in one report (ARMS No. 10862 in the Appendix to this document), three young adult males consumed similar amounts of a dietary supplement containing ephedrine alkaloids, yet only one male experienced serious adverse effects, which resulted in his death (see Police and Medical Examiner's Reports in ARMS No. 10862 in public docket number 95N–0304). This report is illustrative of numerous AER's suggesting an unpredictable pattern and severity of adverse events when consuming ephedrine alkaloid-containing dietary supplements, even when used according to package directions or under ordinary conditions of use. In other cases, some of the adverse events were associated with consumption of relatively low levels of ephedrine alkaloids (e.g., approximately 10 mg or less total ephedrine alkaloids per serving), some occurring shortly after onset of use.

These variations in the occurrence of adverse events relative to duration, frequency, and levels of exposure are suggestive that multiple factors influence sensitivity to ephedrine alkaloid intakes and could be indicative that some of the adverse effects are the result of increased individual susceptibility to the acute or chronic effects of ephedrine alkaloids.

In summary, in reviewing the AER's associated with ephedrine alkaloid-containing dietary supplements, the agency noted a consistency of signs and symptoms across a large number of products, across a range of products with a variety of intended uses, across products with many different formulations, and across a heterogeneous group of individuals with respect to gender, age, and health condition. Generally, the overall pattern of observed results was consistent with stimulant CVS and NS effects, even though not every product showed the same effect or the same seriousness of effect, not every case involved CVS or NS effects, and not all reports were complete or uncomplicated. The patterns of duration of use and dosage

levels suggest patterns of adverse events that are influenced by variations in individual sensitivities. Overall, however, there was a remarkable consistency in the types of signs and symptoms of adverse effects reported. This consistency was recognized by the Working Group (Ref. 27).

The foregoing discussion summarizes the AER's from a descriptive statistical perspective. Many of these reports are summarized in the Appendix to this document. An abbreviated description of all reports is in public docket number 95N–0304. A few examples of experiences of particular individuals are given below.

ARMS No. 11134—A 23-year-old male college student used an ephedrine alkaloid-containing ergogenic product for approximately 2 years, along with several other dietary supplement products. He was previously healthy and was known to have a healthy life style. He was found dead by his sister in the apartment that they shared. The Medical Examiner's report stated that the cause of death was due to ''patchy myocardial necrosis associated with ephedrine toxicity from protein drink containing Ma huang extract.''

ARMS No. 9552—A 35-year-old female, who was on no medications and who had a negative past medical history, developed a non-Q wave myocardial infarction (heart attack) while using an ephedrine alkaloid-containing dietary supplement within the dosage recommended on the label. She used the product for approximately 30 days, stopped for 1 week while on vacation, and then reinitiated the use of the product. About 11 days after restarting the product, she developed acute throbbing, anterior chest pain at rest, with radiation to the left shoulder, numbness of the left arm and hand, diaphoresis (sweating), and shortness of breath. In the hospital, clinical evaluations (electrocardiogram and cardiac enzymes) indicated an acute non-Q wave myocardial infarction, thought to be secondary to coronary artery spasm. Cardiac catheterization showed normal coronary arteries.

ARMS No. 10009—A 35-year-old male took an ephedrine alkaloid-containing dietary supplement (2 capsules at noon, 3 capsules at 4:30 pm). He worked out from 5:30 to 6:30 pm, developing chest pain at 7:30 pm. He was admitted to the hospital with an acute myocardial infarction (by electrocardiogram and cardiac enzymes) and was treated medically. Subsequent cardiac catheterization demonstrated normal coronary arteries.

ARMS No. 11144—A 28-year-old man used an ephedrine alkaloid-containing product for 10 months (1 capsule per day) for energy. His father found him bloody and responding inappropriately. In the emergency department, his blood pressure was 168/90, with a pulse of 116. Results of extensive clinical and laboratory evaluations were all within normal limits. He was diagnosed with syncope and a closed head injury. His neurologist concluded that ''most likely he had a seizure secondary to ephedrine'' from the health food substance he was taking. He was advised to avoid the product and dispose of it. This man was on no other medications and had no significant past medical history. In particular, he never had problems with dizziness or passing out.

ARMS No. 10974—A 19-year-old woman took an ephedrine alkaloid-containing product, one before each meal, three times per day (½ of recommended amount) for 1 month, for weight loss. Her family witnessed seizure activity at mealtime and took her to the emergency room. Evaluations there were essentially normal (CT scan of the head and electroencephalogram or EEG). The neurologist's evaluation found no other risk factors for seizure. No other products had been used, and there was no significant past medical history.

ARMS No. 10088—A 38-year-old female took two products containing ephedrine alkaloids for 4 days, and she developed syncope (light-headedness) and an extremely elevated blood pressure, measured at 180/110. She was seen in the emergency department with severe headache, nausea, and sweating. The consumer had been seen every 3 to 4 months for the 5 years before this event and had no history of high blood pressure. After stopping the products, her blood pressure returned to normal.

ARMS No. 10919—A 49-year-old woman used an ephedrine alkaloid-containing product, 3 capsules three times daily for 3 weeks for weight loss. She developed weakness, dizziness, nausea, vomiting, and palpitations and went to the emergency room, where she was found to have vertigo (type of dizziness), serous otitis media (middle ear inflammation) bilaterally, hypertension (150/102), and elevated liver enzymes. The consumer reported that when she stopped the product, her blood pressure returned to normal without any medical treatment. She did not have a history of high blood pressure.

ARMS No. 10946—A 42-year-old female used an ephedrine alkaloid-containing product, 1 capsule twice daily for 3 days for weight loss. She was also taking vitamin B_{12} and an antioxidant supplement. She developed a rash over her entire body and stopped all three products. She restarted the ephedrine alkaloid-containing product 3 days after the onset of her rash. Three days later, on a visit to her doctor for a nonproductive cough and congestion, she was found to be seriously hypertensive (170/114). She had no history of hypertension and had been seen by her gynecologist 1 week before starting the ephedrine alkaloid-containing product, where a normal blood pressure (120/78) was documented.

2. The Patterns of the Signs and Symptoms of Adverse Events Associated With Ephedrine Alkaloid-Containing Dietary Supplements Are Consistent With the Available Scientific Evidence and Known Physiologic and Pharmacologic Effects of Ephedrine Alkaloids

The observed CVS and NS effects associated with use of ephedrine alkaloid-containing dietary supplements are consistent with the known pharmacologic and physiologic effects of ephedrine alkaloids. Because there is a general paucity of scientific data or other information on the physiologic or pharmacologic properties of ephedrine alkaloids from botanical sources, and particularly from marketed dietary supplement products, FDA reviewed other available evidence on ephedrine and other ephedrine alkaloids for information on their effects. This evidence included data from clinical and animal studies in support of drugs containing a single, synthetic ephedrine alkaloid in a well-defined and characterized product, case reports from the literature of adverse events with ephedrine alkaloid-containing products, and traditional medical uses of ephedrine alkaloid-containing botanicals.

Although there may be some differences in the pharmacokinetic properties of synthetic ephedrine alkaloids used in drug products as compared to the botanical sources of these alkaloids as used in dietary supplements (e.g., differences in enantiomer forms, dissolution, absorption, and bioavailability or differences that result from interactions with other components of the botanical), given that once absorbed, the botanical and synthetic sources of ephedrine alkaloids undergo similar metabolic processes (Refs. 24 and 43), the agency considered it appropriate to rely on evidence from pharmaceutical sources of single ephedrine alkaloids in assessing the effects of botanical sources. This judgment is supported by

the fact that adverse events reported for dietary supplements containing ephedrine alkaloids from botanical sources are similar to those that are reported in the literature for drugs containing an ephedrine alkaloid from synthetic sources. FDA's Working Group agreed that evidence on synthetic sources of ephedrine alkaloids could be considered in evaluating botanical sources (Ref. 27).

Ephedrine and its related alkaloids are known to elicit physiological responses similar to catecholamines (i.e., groups of chemically related neurotransmitters, such as epinephrine, norepinephrine, and dopamine) that have stimulant effects on the sympathetic nervous system and thus are classified as sympathomimetic agents (i.e., agents stimulating the sympathetic nervous system) (Refs. 7, 9 through 13, and 44 through 48). Ephedrine, pseudoephedrine, and norephedrine are naturally occurring sympathomimetic amines in some botanicals. Ephedrine, pseudoephedrine, and norephedrine each have varying effects because of interaction with specific receptors in the human body (i.e., alpha, beta-1, and beta-2 adrenergic receptors) (Refs. 9 through 13). (Table 2 summarizes some of the major receptor effects, and Table 3 summarizes the adrenergic activity of ephedrine, pseudoephedrine, phenylpropanolamine (dl-norephedrine), and norepinephrine.) Some of the physiological roles of alpha receptors are central NS stimulation, vasoconstriction (i.e., narrowing of blood vessels), uterine contraction, centrally mediated cardiovascular depression, and decreased insulin secretion. Alpha receptors also have an effect on the urinary bladder, which can result in urinary retention. The major physiological roles of beta receptors include cardiac (i.e., heart) stimulation and bronchodilation (enlargement of the bronchial or breathing tube secondary to relaxation of bronchial smooth muscle).

TABLE 2.—ADRENERGIC ACTIVITY OF SYMPATHOMIMETIC AGENTS (MODIFIED FROM REF. 9)

Organ/system	Type of effects adrenergic receptors			Other effects
	α	β_1	β_2	
Nervous system (NS)	Central NS Stimulation	.....	.....	Indirect Effects on Neurotransmitters Result in NS Stimulation.
Cardiovascular system	Vasoconstriction	Cardiac stimulation: ..... ↑contractility (force & velocity). ↑heart rate ..... ↑impulse conduction ..... ↑cardiac output ..... ↑O_2 consumption ..... ↑stroke volume ..... ⇄diastolic coronary perfusion time. ⇄ventricular filling ..... ⇄residual (end-systolic) volume.	Cardiac stimulation: ..... ↑heart rate ..... ⇄arteriolar tone ..... ⇄peripheral resistance ..... ⇄diastolic pressure ..... ⇄cardiac afterload ..... vasodilation.	
Other	↑uterine contraction ..... ↑ureter motility & tone ..... pupillary dilation ..... ⇄GI motility & tone ..... ⇄pancreatic secretion (islets/acini). contraction, urinary, bladder, sphincter & trigone.	lypolytic activity ..... ↑renin secretion	bronchodilation ..... ↑insulin secretion ..... muscle & liver glycogenolysis. ⇄GI motility & tone ..... urinary bladder—relaxation of detrusor muscle. relaxation of uterus cerebellum— synaptic remodeling.	

TABLE 3.—ADRENERGIC ACTIVITY OF SYMPATHOMIMETIC AGENTS (MODIFIED FROM REF. 9)

Sympathomimetic agent	α-Receptor effects	β_1-Receptor effects	β_2-Receptor effects	CNS effects
Ephedrine	moderate	strong	strong	strong.
Pseudoephedrine	moderate	moderate	moderate	moderate.
Phenylpropanolamine (dl-norephedrine)	strong	very little	very little	strong.
Norepinephrine	very strong	very little	none	none.

The different types of ephedrine alkaloids exhibit some similar effects but vary in the intensity of these effects (Refs. 10 through 13). For example, ephedrine increases arterial blood pressure in humans both by peripheral vasoconstriction (narrowing of the blood vessels in the periphery of the body) and by cardiac stimulation, resulting in increased heart rate and cardiac output. The magnitude of these cardiovascular responses can vary on an individual basis and may be dependent on a number of factors, including genetic characteristics, a history of certain diseases or conditions, or the use of certain medications. Other actions of ephedrine include stimulation of oxygen uptake and thermogenesis (heat or energy production). Pseudoephedrine is less potent than ephedrine both in its bronchodilatory and vasopressor effects (i.e., effect of elevating blood pressure). It produces about one half the

bronchodilation and one quarter of the vasopressor effects of ephedrine (Refs. 9 and 13).

a. *Physiologic and pharmacologic evidence: cardiovascular effects of ephedrine alkaloids.* The adverse events involving the CVS reported to FDA that are associated with dietary supplements containing ephedrine alkaloids are consistent with the known effects of sympathomimetic agents on the CVS. Cardiovascular effects resulting from the use of sympathomimetic agents are well documented in the literature (Refs. 49 through 52). For example, use of ephedrine has been reported to interfere with the regulation of serum potassium levels (Refs. 53 through 55) and thus may predispose certain individuals to cardiac dysrhythmias (i.e., abnormal heart rhythms) (Refs. 18 and 56); myocardial ischemia (i.e., inadequate circulation of blood and oxygen to the heart muscle); and infarction (i.e., death or damage of heart cells, also called heart attack) (Refs. 57 through 61). Cardiac damage has also been reported with the use of pseudoephedrine and phenylpropanolamine (norephedrine) (Refs. 16, 56, 60, and 62 through 64). Results of several studies on blood pressure effects with the use of ephedrine alkaloids have indicated that individuals with hypertension may be at greater risk of blood pressure elevations with the use of ephedrine (reviewed in (Ref. 64)).

The signs and symptoms observed in the AER's are consistent with the available scientific literature on the effects of ephedrine alkaloids. Serious cardiovascular adverse events are the major cause of death reported in the AER's with the use of ephedrine alkaloid-containing products and primarily involve ischemia (inadequate blood flow) which can cause heart attacks and strokes. These events have occurred in asymptomatic, otherwise healthy young adults with normal coronary or cerebral blood vessels (Ref. 25), a finding also noted with pharmaceutical preparations of ephedrine alkaloids (Refs. 60, 61, and 65), where vasospasm with subsequent ischemia is a proposed mechanism of tissue injury. Besides causing damage by affecting blood flow, sympathomimetic agents, such as ephedrine, can damage the heart and other tissues or organs by other mechanisms. Cardiomyopathy (i.e., disease of the heart muscle) related to catecholamine mediated cytotoxicity (cell damage) has been reported with chronic use of ephedrine alkaloids (durations of use generally at or above the recommended dose that occur over many months or years) (Refs. 62 and 66 through 68). Fatal cardiomyopathies have also been reported with chronic use of ephedrine alkaloid-containing dietary supplements (ARMS No. 11134 in Ref. 149a).

Ephedrine and pseudoephedrine have been implicated also in stroke secondary to intracranial (i.e., inside the brain) and subarachnoid (i.e., underneath the membrane that covers the brain and spinal cord) hemorrhage and vasculitis (i.e., inflammation of blood vessels), as well as in ischemic strokes (Refs. 9 and 69 through 71), particularly when used in combinations with phenylpropanolamine (norephedrine) or caffeine (Refs. 65 and 72 through 78) or in the presence of monoamine oxidase inhibitors (MAOI) (Ref. 72). These effects are noted to be similar to the necrotizing angiitis (severe inflammation with destruction of the blood vessels) seen in chronic amphetamine abuse (Refs. 16, 74, and 77 through 79).

b. *Physiologic and pharmacologic evidence: NS effects of ephedrine alkaloids.* The adverse events involving the NS reported to FDA that are associated with dietary supplements containing ephedrine alkaloids are consistent with the known effects of sympathomimetic agents on the NS. These effects, such as seizure (Refs. 63, 65, and 80), psychosis, and mania (Refs. 81 through 99), have been reported with the use and the abuse of ephedrine alkaloids. More recently, a case report in the scientific literature reported ephedrine-induced mania associated with the use of a botanical dietary supplement (Ref. 100).

Neuropsychiatric effects reported in AER's related to ephedrine alkaloid-containing dietary supplements also are consistent with the known physiologic and pharmacologic actions of ephedrine alkaloids documented in the scientific literature. Mania and psychosis have occurred in individuals without identifiable risk factors who have used these products, as well as in people who used them who had possible predisposing factors, such as a personal history of mood disorders (i.e., depression or manic depression), a family history of manic depression, or concurrent use of products that increase sensitivity of an individual to the effects of ephedrine alkaloids (see Table 4). AER's noting neuropsychiatric adverse effects in persons using non-MAOI antidepressant drugs concurrently with dietary supplements containing ephedrine alkaloids are consistent with a report of the serotonin syndrome associated with the concurrent use of serotonin reuptake inhibitors (a new class of antidepressant drugs) and OTC cold remedies containing pseudoephedrine (Ref. 101).

TABLE 4.—FACTORS INFLUENCING SENSITIVITY TO SYMPATHOMIMETIC AGENTS

Factor	Examples
Age	Children, elderly.
Genetics	Metabolizer genotype; adrenergic receptor genotype and numbers.
Physiological states	Hyperdynamic (exercise), underweight.
Dieting practices	Severe caloric or fluid restriction.
Medications and food	MAOI, methyldopa, β-receptor blocking agent, caffeine or other stimulants.
Diseases or health-related conditions	Heart disease, thyroid disease, diabetes, renal disease, high blood pressure, depression, psychiatric conditions, glaucoma, prostate enlargement, seizure disorder.
Duration of use	Vascular spasm; stroke and myocardial infarction may influence the type and severity of adverse events in the sensitive individual.

c. *Variability in individual responses to ephedrine alkaloids.* The unpredictability of individual responses to ephedrine alkaloid-containing dietary supplement products, as reported in AER's, is also consistent with what is known about the physiological and pharmacological properties of these alkaloids (Refs. 7, 10 through 12, 39 through 41, and 48). Individual variability in the effects of ephedrine has been reported in several clinical investigations (Refs. 5 and 102 through 104). The marked sensitivity of some individuals to the effects of ephedrine has been recognized in the Western scientific literature almost from the time that ephedrine was introduced as a

therapeutic agent in the mid-1920's (Refs. 5 and 102). Two early studies by different investigators recommended a 10 mg initial oral test dose to assess the individual's sensitivity to sources of ephedrine (Refs. 5 and 102).

Factors that appear to influence individual susceptibility to sympathomimetic agents are diverse (see Table 4) and are not yet well defined by biological bases. These factors include genetics, particularly those genes controlling metabolic functions; receptor numbers and types; gender; age; and certain physiological states or disease conditions (reviewed in Refs. 39 through 42). In addition, the dosage and duration of use may influence the effects seen with ephedrine alkaloids, as tachyphylaxis (i.e., decrease or diminution of some effect) is known to occur with chronic use of these agents (i.e., there are decreases in certain effects with chronic use that are thought to be due to occupation of all adrenergic receptor sites; discontinuation of ephedrines for a few days results in receptor availability and receptor mediated effects). An example of tachyphylaxis could be tremor or insomnia, which occurs soon after starting ephedrine alkaloid-containing products but which may resolve in certain individuals with continued use of ephedrine alkaloids.

d. *Clinical trials using ephedrine in the treatment of obesity.* Although many dietary supplements containing ephedrine alkaloids are marketed for weight loss or energy purposes, there is a paucity of meaningful data on the safe use of these products for this purpose.

A number of controlled clinical trials reported in the scientific literature evaluated the effects of pharmaceutical preparations of ephedrine, either singly or combined with caffeine or aspirin, on weight loss in the treatment of obesity (Refs. 105 through 119). While the primary purpose of these trials was to evaluate efficacy of ephedrine for purposes of weight loss in grossly obese individuals, these clinical trials also document that clinically significant adverse effects can occur in populations with no known risk factors with the use of ephedrine, and that synergistic adverse effects can result when ephedrine and caffeine are combined. The patterns and types of the adverse effects reported in these trials are consistent with the known effects of sympathomimetic agents, that is, they mainly involved NS and CVS effects. A summary of these studies follows. (In this document, the agency makes no evaluation or judgment of the effectiveness of the use of ephedrine in the treatment of obesity.)

A Danish group of researchers investigated the usefulness of ephedrine and caffeine alone and in combination for the treatment of obesity (Refs. 105, 106, and 112). One hundred and eighty subjects were randomized to one of four treatment groups: (1) Ephedrine—20 mg, (2) ephedrine—20 mg and caffeine—200 mg, (3) caffeine—200 mg, and (4) placebo control. The treatments were administered three times a day for 24 weeks in conjunction with a defined low calorie diet. One hundred and forty-one individuals completed the trial. Subject withdrawals were reported to be equally distributed across the four groups with no statistical differences among the groups. More side effects were noted in the treatment groups compared to the placebo control group in both those subjects continuing in, and those withdrawing from, the trial. Study results showed that 60 percent of the ephedrine and caffeine treatment group, 44 percent of the ephedrine treatment group, and 36 percent of the caffeine treatment group experienced side effects compared to 24 percent of the placebo control group. These results were statistically significant ($p<0.05$) (Ref. 105). This study showed that there was a possibility of rebound symptoms (symptoms occurring as a consequence of withdrawal of an agent, especially headache and fatigue) once the treatment was stopped. Rebound symptoms were seen most in the ephedrine and caffeine treatment group but also occurred in the ephedrine alone group (Refs. 105 and 106).

Astrup et al. enrolled 127 of the subjects completing the above clinical trial into an open label study where all subjects received the same treatment (diet and ephedrine plus caffeine) for 24 weeks (Refs. 106 through 108). Five of the 38 subjects that withdrew or dropped out of this study did so because they experienced adverse drug reactions (NS and CVS effects). Adverse drug reactions occurred in 102 subjects during weeks 1 through 24 of the open trial. Most symptoms (75 percent) started during the first 4 weeks of treatment and lasted about 4 weeks. Symptoms related to the CVS were primarily palpitations and tachycardia. The most frequent NS symptoms were tremor, agitation, insomnia, increased sweating, and nervousness.

Breum et al., in another clinical trial in which the effects of ephedrine plus caffeine (EC) were evaluated, conducted a randomized, double blind, controlled 15 week clinical trial comparing the effects of EC to that of dexfenfluramine (DF), a serotoninergic agonist, in the treatment of obesity (Ref. 113). Fifty four percent of the subjects in the EC group compared to 43 percent of the DF group experienced adverse reactions. The majority of these occurred within the first 4 weeks. At week one, 38 percent of the EC group subjects experienced adverse drug reactions compared to 30 percent in the DF group. NS effects (particularly insomnia and agitation) were statistically increased ($p < 0.05$) in the EC treatment group (46 percent) compared to the DF group (26 percent), whereas gastrointestinal adverse effects were significantly increased in the DF group. Eight percent of the EC group reported cardiovascular symptoms. All symptoms remitted after cessation of the trial drugs.

The above studies demonstrate that adverse effects can occur with the use of ephedrine in the treatment of obesity even in carefully designed and conducted, physician-monitored clinical trials and even in persons prescreened to be in good health, free of known risk factors, and not using medications or other products known to adversely interact with ephedrine-like drugs. Furthermore, the study population of obese individuals is recognized to be less sensitive to the effects of sympathomimetic agents than the general population (Ref. 120). Certain of these studies also evidence that there is an increased frequency of adverse effects occurring in lean subjects, secondary to sympathetic stimulation, compared to obese subjects that is unrelated to dose per body weight (Ref. 119). Thus, these studies suggest that the general population may be more sensitive to the effects of ephedrine alkaloids than the obese population.

There are a number of recognized limitations inherent in these published trials, including those associated with study design, methods, and conduct (e.g., small number of subjects enrolled in these trials, narrow targeted populations, short evaluation periods, and selective presentation of data are among the concerns) as are the multiple publications of the same data. Yet despite these factors, the adverse effects observed in these studies remain a cause for concern, although these factors make it difficult to identify subpopulations that may be particularly sensitive to the effects of ephedrine or to identify adverse effects that occur infrequently. These studies were carefully monitored, so that subjects were withdrawn from the study when adverse effects became evident. Therefore, although the observed adverse effects in these studies were not as severe or as serious as some observed with dietary supplement use (e.g., heart attacks, seizures, strokes), they are indicative of the potential for

greater risk with continued use. Moreover, their occurrence is remarkable given the careful prescreening of study subjects such that high risk persons were not included in the study.

The greatest limitation, however, is that these studies were designed to evaluate the effectiveness of ephedrine in the treatment of obesity. They were not designed to test the safety of the use of ephedrine in the obese, or any other population (Ref. 121), or to test its safety under the conditions under which marketed dietary supplements containing sources of ephedrine alkaloids are used. Therefore, these study results cannot be used to definitively demonstrate safety, or the lack of safety, of ephedrine alkaloid-containing supplements for use by the general population. Nonetheless, despite the shortcomings of these studies, the results raise serious concerns about the safety of using ephedrine, from any source, including dietary supplements, in both obese individuals and the general public in nonmedically monitored situations.

e. *Other physiologic and pharmacologic effects.* Some of the adverse events reported to FDA that were unrelated to the CVS and NS also bear a recognized relationship to the known physiologic and pharmacologic effects of ephedrine alkaloids. For example, urinary retention, particularly in males with no history of prostatic hypertrophy (enlargement of the prostate gland), has been associated with the use of ephedrine (Refs. 102, 103, and 122 through 124). Urinary retention has a well recognized relationship with urinary tract infections, which have been reported to FDA with the use of products containing ephedrine alkaloids. Myopathy (disease of muscle), besides being reported for the heart (Refs. 62 and 66 through 68), is also recognized to involve skeletal muscles and may result in acute renal failure (Ref. 125). Certain gastrointestinal adverse effects, including impaired colonic motility and ischemic colitis, have been associated with the usage of amphetamines (Refs. 102 and 126). Similarly, ischemic colitis has also been reported with the usage of a long-acting decongestant containing pseudoephedrine (Ref. 127). Additionally, acute hepatitis (inflammation in the liver) has been associated with the use of a Chinese medicinal product containing Ma huang (Ref. 128).

Other types of adverse effects, such as the reports of dermatologic reactions, while not known to be related to the recognized physiologic or pharmacologic effects of ephedrine alkaloids, are consistent with adverse effects reported in published case reports. For example, there are more than 11 published case reports, at least 12 patients, of systemic dermatologic reactions, including rashes occurring in a particular distribution on the body, contact dermatitis (inflammation of the skin resulting usually from local contact with a substance), a toxic shock-like syndrome, angioedema (extreme swelling of tissues and structures of the body secondary to leaking of fluids from capillaries (small blood vessels)), and erythematous (reddish) rash and subsequent desquamation (loss of part of the skin surface) that occurred with the use of ephedrine or pseudoephedrine (Refs. 114 and 129 through 138).

Concerns about toxicity to the fetus with maternal exposure to ephedrine alkaloids during pregnancy remain unresolved. Increased fetal heart rate has been associated with maternal use of pseudoephedrine (Ref. 139). In addition, the administration of intramuscular ephedrine to treat maternal hypotension has been associated with increases in fetal heart rate and beat-to-beat variability (cited in Ref. 139). Certain animal studies also raise concern about potential teratogenic effects that may be caused by the use of ephedrine during pregnancy (Refs. 140 through 143). Potential toxicity for a breast-fed infant whose mother is using a dietary supplement containing ephedrine alkaloids is unknown, but toxicity has been reported in a breast-fed infant whose mother had been taking a long-acting oral decongestant containing d-isoephedrine for the relief of allergy symptoms (Ref. 144).

Little is known about the potential consequences of long term use of ephedrine alkaloids, other than the risk of cardiomyopathy as stated above. Park et al., however, recently implicated β-adrenergic agents like ephedrine in the etiology of a type of lung cancer, particularly in persons simultaneously exposed to carcinogenic environmental factors such as smoking (Ref. 145). This report indicates the need for long-term followup to adequately assess the risks associated with product use, as well as the importance of particular group characteristics (e.g., smoking status) in evaluating risk.

f. *Traditional uses of botanical sources of ephedrine alkaloids: adverse effects.* In the traditional medicinal use of *Ephedra,* the raw botanical was administered, either alone or more commonly combined with other specific botanicals, in the form of a water infusion (tea), three times a day. Traditional treatment was prescribed by a trained health practitioner based on the evaluation of a particular patient and was predominately for short term use. Commonly used dosages of the raw botanical ranged from 1.5 to 9 grams (g), generally averaging 5 to 6 g of *Ephedra* per dose (Refs. 14 and 146). Tyler has estimated that a tea made from 2 g of the raw botanical *Ephedra* (containing 1.25 percent ephedrine) will yield a dose of 15 to 30 mg ephedrine (cited in Ref. 147). Thus, use of 5 to 6 g of the raw botanical *Ephedra,* an average amount used in a tea could yield a dose of ephedrine ranging from approximately 38 mg to 75 mg.

FDA has no knowledge of any systematic collection of morbidity and mortality data on individuals treated with *Ephedra* in traditional medicine. *Ephedra* was historically considered a medium or middle class herb, meaning that recognized toxicities could be associated with its use (Refs. 14, 146, and 148). Several reference texts, in fact, list precautions and contraindications for the use of the botanical *Ephedra* in traditional medicinal preparations (Refs. 14 and 146). Another reference warns against overdosage (Ref. 25).

While there is a paucity of data in the scientific literature on the safety of the use of *Ephedra,* several scientific references report adverse effects associated with the use of *Ephedra.* One early study in the United States reported two cases of urinary retention in men aged 56 and 65 years. These men all noted bladder pain and difficulty in voiding which developed after one to three doses of a fluid extract of *Ephedra.* The symptoms resolved after the use of the extract was discontinued. More recently, a published case report notes the occurrence of erythroderma associated with the use of an herbal product containing Ma huang which was obtained from a Chinese herbalist for the relief of cold-like symptoms (Ref. 138). The woman who was the subject of this report had a history of similar episodes following usage of OTC cold preparations containing ephedrine alkaloids. These references document that adverse effects occurred with the traditional use of *Ephedra,* and that these effects are consistent with effects occurring with modern pharmaceutical preparations of synthetic ephedrine.

3. The Relationship is Temporally Correct

One possible source of serious error in evaluating observational data, such as that found in FDA's postmarketing surveillance system, is the potential for inappropriately assuming that a cause and effect relationship exists between a

particular exposure and a particular adverse event without evaluating the true relationship of the adverse event to the exposure. Unless there are data that ensure that there is the correct temporal relationship between exposure and effect (i.e., that the adverse effects follow exposure), there is a potential for serious misinterpretation of data. To evaluate this potential source of serious error, FDA evaluated the AER's to determine whether there was clear evidence of the correct temporal sequence having occurred. FDA found evidence of the correct relationship in the AER's that it received (see, e.g., ARMS Nos. 10088, 8475, 9747, and 11112).

Further support that the temporal relationship is correct can be found in clinical studies that described the pharmacological and physiological effects of different ephedrine alkaloids and in the clinical trials with obese subjects.

4. There is Other Evidence, Even in the Absence of Controlled Trials, Such as Evidence of Dechallenge That Suggests a Causal Relationship Between the Use of Ephedrine Alkaloid-Containing Dietary Supplements and Adverse Events

Causality is most readily demonstrated in well-designed and conducted clinical trials, in which the multiple factors that may influence study results and interpretations can be controlled. However, evidence of causality can be inferred from observational studies, including individual case reports, particularly where there is evidence of positive dechallenge and rechallenge, that is, where, when the consumer stopped using the product, the signs and symptoms resolved or improved, and when the consumer began using the product again, the symptoms reoccurred. Although many of the AER's did not provide enough information to adequately evaluate these questions, over 26 percent of AER's provided information suggesting successful dechallenge, and 4 percent of reports provided information of rechallenge, suggesting that the product was the direct cause of the adverse event. A number of the previously described cases are particularly good examples of positive dechallenge in that symptoms resolved spontaneously on cessation of use of the product without medical treatment (see Arms Nos. 10088, 11065, and 11112 in the Appendix to this document).

Furthermore, some specific AER's suggest that a pattern of starting and stopping use of dietary supplements containing ephedrine alkaloids may increase an individual's susceptibility to experiencing adverse events as has been suggested in reviews of adverse events occurring with the use of phenylpropanolamine (Ref. 73). One case described above, ARMS No. 9552, in which a woman suffered a heart attack soon after she restarted using an ephedrine alkaloid-containing product, may be an example of such increased sensitivity.

Thus, FDA tentatively concludes that there is evidence of dechallenge and rechallenge from the AER's that supports a causal relationship between the ingestion of ephedrine alkaloids and the types of CVS and NS and other effects observed with use of the ephedrine alkaloid-containing dietary supplement products. Additional support for this conclusion is also provided in the published clinical trials in the treatment of obesity described above.

5. A Biologically Plausible Explanation for the Adverse Events

Considering the totality of the available information, FDA tentatively concludes that the available evidence strongly supports that the adverse effects that are occurring with the use of dietary supplements containing ephedrine alkaloids are caused by the ephedrine alkaloids. This tentative conclusion derives from the previous discussions in this document. The observed adverse effects predominately involve the CVS and NS and are consistent with the known physiological and pharmacological effects of ephedrine alkaloids noted in medical/pharmacological texts. Furthermore, similar patterns of CVS and NS effects have been documented both in anecdotal reports in the scientific literature and in the published results of controlled clinical trials using pharmaceutical preparations of various ephedrine alkaloids. The available data further suggest that these types of adverse events should be anticipated and expected with the use of ephedrine alkaloid-containing products by the general population.

D. Additional Concerns

The agency is aware of a number of factors related to currently marketed dietary supplements that may contribute to the likelihood of adverse events but that the available data are inadequate to evaluate fully. These factors weighed heavily on the minds of many members of the Food Advisory Committee as they discussed the public health concerns associated with the use of these products. These factors include:

(1) The size of the population that is susceptible to experiencing adverse events with the use of ephedrine alkaloids, because there are neither good data on the number and pattern of supplement users in the United States nor good data on the full range of characteristics that cause or increase risk. Nonetheless, the potential population at risk is quite large if one considers the following likely risk factors:

(a) The large number of persons who have diseases or conditions, or who are at risk for such conditions, for whom the use of ephedrine alkaloid-containing dietary supplements is inappropriate (Table 5).

TABLE 5.—IDENTIFIABLE AT RISK POPULATION WITH USE OF EPHEDRINE ALKALOIDS

Disease or condition	Estimated number of affected persons in the United States (in millions)
Cardiovascular disease	50 (Ref. 158).
Hypertension	50 (Ref. 158).
Kidney trouble	3.5 (Ref. 159).
Prostate disease	2.6 (Ref. 159).
Glaucoma	2.4 (Ref. 160).
Diabetes	16 (8 million undiagnosed) (Ref. 161).
Depressive, anxiety or schizophrenic disorders	42.3 (Ref. 162).
Thyroid disease	11 (6 million undiagnosed) (Ref. 163).
Pregnancy	4 (each year) (Ref. 179).

(b) The large number of factors that may increase susceptibility or sensitivity to the effects of ephedrine alkaloids and other sympathomimetic agents (Table 4). These variables include gender, age, genetics, certain physiologic states, and the use of certain products (e.g., foods and drugs) (Ref. 25).

(2) The potential for interactive and unpredictable effects from the mixture of ephedrine alkaloids found in botanical sources, which may serve to increase the likelihood, frequency, or severity of an adverse event. Unlike drugs which contain only a single, well-characterized ephedrine alkaloid, botanical sources contain a mixture of these alkaloids. The potential for interactive effects among these alkaloids is likely but largely unknown (Ref. 25).

(3) The potential for other ingredients in the dietary supplement products to interact with the ephedrine alkaloids to increase the likelihood or severity of an adverse event (Ref. 25).

(4) The natural or formulation variations in levels and relative proportions of the ephedrine alkaloids in marketed dietary supplement products and the resultant risk for persons who can tolerate one level or mixture but who unknowingly are exposed to different levels or mixtures because they change brands, or because the composition of the brand that they typically use is altered (Ref. 25).

(5) The formulations of the products themselves (including the numbers, types, and forms of ingredients used in the product and the form of the final product) may influence the likelihood, frequency, or severity of adverse effects because product characteristics may influence dissolution, absorption, bioavailability, and metabolism of active and inactive ingredients in the product and thus influence the effects of the product (Ref. 25).

E. General Summary and Tentative Conclusions

FDA has received more than 800 AER's involving more than 100 dietary supplement products. Among these products the most common and consistent finding is the presence of ephedrine alkaloids. The products associated with these adverse events are marketed in diverse formulations and for a variety of uses.

Sympathetic nervous system and cardiovascular system stimulant effects account for the majority of the reported adverse events associated with dietary supplements containing ephedrine alkaloids. These effects include heart attack, stroke, seizure, chest pain, psychosis, anxiety, nervousness, tremor, and hyperactivity (Refs. 25 and 27). The type and patterns of these adverse effects are consistent with the CVS and NS effects known and expected to occur with the use of sympathomimetic agents, such as the ephedrine alkaloids. The known physiological and pharmacological activities of ephedrine alkaloids and the adverse events that have occurred in controlled clinical trials using ephedrine corroborate this conclusion. The biological plausibility of these types of adverse events occurring with the use of ephedrine alkaloids, the temporal relationship between the use of the dietary supplements and the onset of the adverse events, and the evidence of dechallenge and rechallenge also support a causal relationship between the use of ephedrine alkaloid-containing products and subsequent adverse events.

Both the Working Group and the Food Advisory Committee reviewed the available data and information on the occurrence of adverse events associated with the use of dietary supplements containing ephedrine alkaloids in certain individuals. The Working Group was specifically asked whether the available information contains sufficient evidence to demonstrate that the use of dietary supplements containing ephedrine alkaloids may cause consumers to experience serious adverse events. The Working Group concluded that it was. Although not asked this question, those members of the Food Advisory Committee who addressed the question agreed with the Working Groups's conclusion.

Thus, FDA tentatively concludes that there is a consistent, large, and growing body of evidence that establishes a causal association between the use of ephedrine alkaloids and subsequent adverse events. The agency also tentatively concludes that the use of ephedrine alkaloid-containing dietary supplements is associated with a serious and significant public health concern because of the nature of the adverse events and the size of the population at risk.

III. The Proposed Regulation

A. The Scope of This Proposal

This proposal applies to dietary supplements containing one or more ephedrine alkaloids and related alkaloids, including those from the botanical species *Ephedra sinica* Stapf, *Ephedra equistestina* Bunge, *Ephedra intermedia* var., *tibetica* Stapf, *Ephedra distachya* L., and *Sida cordifolia* or their extracts.

Conventional food products that contain ephedrine alkaloids, including snack bars, cookies, and beverages, are not covered by this proposal. Conventional food products are subject to section 409 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 348) and, given the adverse events associated with the use of ephedrine alkaloids, these substances are unapproved food additives when used in conventional foods.

Use of botanical sources of ephedrine alkaloids in traditional herbal therapies is beyond the scope of this proposal. Although several *Ephedra* species (including those considered as Ma huang) have been reported to have a long history of use in traditional Asian medicine for the treatment of the symptoms of colds, to relieve respiratory symptoms, and to regulate water metabolism (Refs. 4, 6, 14, and 146), products bearing claims evidencing that they are intended for therapeutic use are regulated as drugs under the act.

This proposal also does not cover OTC or prescription drugs that contain ephedrine alkaloids. Ephedrine is approved as an active ingredient in oral OTC bronchodilator drugs for use in the treatment of medically diagnosed mild asthma (21 CFR 341.76). However, in the **Federal Register** of July 27, 1995 (60 F.R. 38643), FDA proposed to amend the final monograph for OTC bronchodilator drug products to remove the ingredients ephedrine, ephedrine hydrochloride, ephedrine sulfate, and racephedrine hydrochloride and to classify these ingredients as not generally recognized as safe and effective for OTC use.

FDA issued the proposal to amend the final monograph for OTC bronchodilator products in response to a request from the U.S. Department of Justice, Drug Enforcement Administration (DEA), to restrict OTC availability of ephedrine because of its illicit use as the primary precursor in the synthesis of the controlled substances methamphetamine and methylcathinone. The agency also issued the proposal because of new information that showed that misuse and abuse of OTC ephedrine drug products can cause potential harm, and because of comments made by FDA's Pulmonary-Allergy Drugs Advisory Committee and the Nonprescription Drugs Advisory Committee. FDA is currently evaluating public comments to that proposal and will be addressing this subject in a future issue of the **Federal Register**.

B. Rationale for the Proposal

It is incumbent upon the agency to respond to the concerns raised by the number, seriousness, and pattern of adverse events associated with the use of ephedrine alkaloid-containing dietary supplements. Given the AER's, the case reports in the scientific literature, controlled clinical trials, published reports of adverse effects with traditional uses of ephedrine alkaloid-containing botanicals, and other data, it is apparent that there are serious and well-documented public health risks attendant to the use of ephedrine alkaloids in marketed dietary supplement products, and that the agency needs to propose actions to address these risks.

Over the years, FDA has employed a variety of strategies in addressing food ingredients that created significant public health risks. In cases where small subpopulations have faced serious, even potentially deadly, risks because of ingredients with allergic potential (e.g., nuts and shellfish), FDA has required that the presence of the allergen be declared on the food label so that consumers who are at risk can avoid products that contain the problem ingredient (§ 101.4 (21 CFR 101.4)). In other cases where a food or food ingredient has presented special health risks to consumers under certain use conditions, the agency has required warning label statements to ensure that consumers are alerted to the potential health hazards associated with use of the product. For example, FDA has required a special warning statement to appear on the label of protein products intended for use in weight reduction, stating in part that very low calorie protein diets may cause serious illness or death (§ 101.17(d) (21 CFR 101.17(d))). In other cases, e.g., the proposed regulations for poisonings in young children because of high intakes of iron-containing dietary supplements, the agency was concerned that, for high potency products, warning labels alone would not be effective in preventing serious harm. Therefore, the agency has decided to require, at least in some cases, warning labels plus special packaging requirements to reduce the risk of serious harm (Ref. 150).

In other cases, where a substance contained in a food may be harmful to health, it has been the agency's policy to define a level at which the harmful substance may render the food adulterated. For example, to address the public health problem of histamine poisoning associated with the consumption of certain fish, the agency issued guidance on the level of histamine at which FDA is likely to take action against the fish because it is adulterated (Ref. 151). Moreover, in § 109.4(b) (21 CFR 109.4(b)), the agency has said that it will establish regulatory limits that represent the level at which an added poisonous or deleterious substance adulterates a food within the meaning of section 402(a)(1) of the act (21 U.S.C. 342(a)(1)).

The agency has attempted to be flexible and practical in tailoring its strategy for dealing with public health risks, taking into account the nature and type of the risk and the potential effectiveness of various alternative approaches. In the case of ephedrine alkaloids in dietary supplements, there are many factors and underlying etiologies that can influence individual sensitivity to these substances. Some of these factors are easily identified or readily controlled; many are not. Factors that are known to influence the likelihood, frequency, and severity of adverse events associated with the use of sympathomimetic agents, including ephedrine alkaloids, include genetics, age (e.g., children and the elderly are at increased risk), preexisting conditions (e.g., kidney disease, heart disease, hypertension, diabetes, thyroid disease, glaucoma, and enlarged prostate), pregnancy, concurrent use of medications (e.g., MAOI, methyldopa), or excessive consumption (see Table 4) (Refs. 39 through 42, 152, and 153). Other factors that may increase an individual's susceptibility to experience adverse events with the use of ephedrine alkaloids include exercise, body size (i.e., lean and normal weight individuals appear to be more susceptible than obese individuals), and dietary intake (i.e., severe caloric and fluid restrictions increase the likelihood of adverse events) (Refs. 39, 42, 119, and 154 through 156).

Significantly, however, many adverse events associated with ephedrine alkaloid-containing dietary supplements occur in individuals who have no apparent risk factors, or who are unaware that they are at risk. Additionally, approximately 40 percent of the reported adverse events occur with the first use or within 1 week of first use, providing little or no warning to consumers of potential risk (see Figure 3). The agency tentatively concludes, therefore, that neither disclosure of the presence of ephedrine alkaloids on the product label nor the use of a warning statement, alone, will be sufficient to protect consumers because many individuals are not aware, and are unable to determine, that they are at risk from consuming ephedrine alkaloids, and serious adverse events may occur on the first use or with very short-term use.

Therefore, the agency has tentatively determined that several measures are needed if the observed adverse events associated with the use of ephedrine alkaloid-containing dietary supplements are to be effectively addressed. These measures are discussed below.

C. Proposal for Dietary Supplements Containing Ephedrine Alkaloids

1. Dietary Ingredient Limit for Ephedrine Alkaloids: Per Serving Basis

One possible strategy for addressing the significant number of adverse effects associated with ephedrine alkaloids in dietary supplements is to restrict the level of the ephedrine alkaloids in these products. In considering this possibility, FDA evaluated two issues: (a) Is there a level at which ephedrine alkaloids cause safety concerns; and (b) if there is, will restricting dietary supplements from containing ephedrine alkaloids at or above that level be adequate, alone, to protect the public health, or will additional steps be necessary.

In considering these questions, FDA evaluated the evidence that provides information on the adverse effects of ephedrine alkaloids that is most relevant to the uses and formulations of marketed dietary supplement products: (a) The published findings from the clinical studies investigating the use of ephedrine for weight loss for the treatment of obesity, and (b) the numerous AER's associated with the consumption of dietary supplements containing ephedrine alkaloids.

First, the agency reviewed clinical trials that have been performed to explore therapeutic uses for ephedrine alone and in combination with other pharmaceutical substances (see earlier discussion in section II.C.2.d. of this document (Refs. 105 through 119)). Information from these trials show that 20 mg ephedrine per dose can cause adverse events to occur in a significant percentage of obese persons (up to 60 percent) prescreened to be free of known risk factors while using these products for a relatively short time (i.e., most adverse events occurred during the first 4 weeks of use). Thus, these studies establish that 20 mg per serving of ephedrine presents potential risks for a subpopulation of morbidly obese persons but provide no information on risk at levels below 20 mg per serving for obese persons. These studies also provide no information on risk at levels below 20 mg per serving for use by persons in the general population (e.g., lean or moderately overweight persons), who are known to be more sensitive to

sympathomimetic substances like ephedrine alkaloids than are the morbidly obese persons who constituted the study population (see section II.C.2.d. of this document). FDA is not aware of any well-designed and conducted studies that evaluate the risks of intakes of ephedrine levels below 20 mg per serving in any population group.

Second, FDA, through its postmarketing surveillance program, has found consistent patterns of adverse events across a broad range of marketed dietary supplement products that contain a variety of ephedrine alkaloid levels per serving. FDA's laboratory analyses of the ephedrine alkaloid levels in the small number of available dietary supplement products that consumers who suffered adverse events turned over to the agency showed that these adverse events were related to ephedrine alkaloid levels from approximately 1 to over 50 mg per serving (Ref. 149). These data, as well as analytical data from samples collected from the marketplace after FDA received AER's from consumers who no longer possessed the product, show a pattern of clinically significant adverse events, including neuropsychiatric effects (e.g., severe depression, seizure), malignant (i.e., extremely high) blood pressure, and myocardial necrosis (i.e., death of the heart muscle) with subsequent cardiac arrest and death, with the use of ephedrine alkaloids at levels approaching and above 10 mg per serving (e.g., seven reports of clinically serious adverse events were associated with products that contained 10 to 15 mg per serving) (Ref. 149a). Clinically significant adverse events were also reported with the use of ephedrine alkaloids at levels that exceeded this range.

FDA has also received a few reports of adverse events, some clinically significant, including tremor, extremely high blood pressure, severe headache, nausea, chest pain, increased heart rate, and insomnia, associated with the use of ephedrine alkaloids at levels below 8 mg (e.g., 2 to 8 mg ephedrine alkaloids per serving) (Ref. 149a). The true clinical significance of these levels of ephedrine alkaloids is difficult to interpret because of the lack of the data (e.g., too few reports with analysis to identify a pattern of clinically serious adverse events at any specific level). Thus, the available information from the AER's and the scientific literature does not provide sufficient data to adequately evaluate risk below approximately 10 mg per serving.

Given the available evidence, it is difficult to ascertain whether there is a threshold level of ephedrine alkaloids below which the general population and susceptible individuals will not experience serious adverse events. The shape of an intake-response curve for any particular adverse effect related to ephedrine alkaloid intakes is not known. In the absence of data that allow a systematic evaluation of intakes of ephedrine and other related alkaloids below 10 mg per serving, it is not possible to adequately define or describe the potential risks and at-risk groups from ephedrine alkaloids. However, the available data, including the AER's and the known physiological and pharmacological effects of ephedrine, provide convincing evidence that clinically serious adverse events will occur at intake levels above 10 mg ephedrine alkaloids per serving.

FDA recognizes, however, that this 10-mg level is also subject to some uncertainty because of such factors as intra-assay variabilities (i.e., difference in analytical results from one run to the next with the same method), natural variabilities in the alkaloid content of botanical ingredients, variations in formulation levels from batch to batch, and inaccuracies in the amounts reported to be taken by consumers. When these sources of variability are considered, given that they are likely to be additive, the range around the 10 mg per serving estimated intake can be expected to deviate by ±10 to 20 percent. Thus, FDA tentatively concludes that the life-threatening adverse events associated with the use of ephedrine alkaloids can reasonably be expected to occur at intake levels as low as 8 to 9 mg ephedrine alkaloids per serving. However, given the limitations in the available data, the agency requests comments on whether it is more appropriate to focus on the 10 mg level.

Based on the available evidence and the likely sources of measurement error around estimated intake levels, the agency tentatively concludes that the use of dietary supplements containing 8 mg or more ephedrine alkaloids per serving may render the dietary supplement injurious to health. The agency also tentatively concludes that consumption of dietary supplements that contain this level or more of ephedrine alkaloids presents a significant and unreasonable risk of illness or injury under the conditions of use recommended or suggested in the labeling or under ordinary conditions of use, and that, therefore, products that contain this or higher levels of ephedrine alkaloids are adulterated. [1]

To reflect this tentative conclusion, FDA is proposing to adopt § 111.100(a)(1) which states that dietary supplements that contain 8 mg or more ephedrine alkaloids (the total of ephedrine, pseudoephedrine, norpseudoephedrine, norephedrine, methylephedrine, methylpseudoephedrine and related alkaloids) per single serving shall be deemed to be adulterated under section 402(a)(1) and (f)(1)(A) of the act. FDA is proposing to adopt this provision under sections 402(a)(1), (f)(1)(A), and 701(a) (21 U.S.C. 371(a)) of the act.

Under section 402(a)(1) of the act, a food, including a dietary supplement, is adulterated if it bears or contains any added poisonous or deleterious substance that may render it injurious to health. Section 402(f)(1)(A) of the act provides that a dietary supplement is adulterated if it, or one of its ingredients, poses a significant or unreasonable risk of injury or illness when used as directed or under ordinary conditions of use. Under section 701(a) of the act, FDA has authority to issue regulations for the efficient enforcement of the act. These sections authorize FDA to issue a regulation that establishes a level of ephedrine alkaloids that, the available evidence makes clear, will render a dietary supplement adulterated as a matter of law.

FDA tentatively concludes that such a regulation will advance the purposes of the act in two significant ways. First, it will 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. Second, it will make clear that if products that contain higher levels of ephedrine alkaloids are marketed; such products will be considered unsafe and adulterated and will be subject to all the relevant sanctions under the act.

Eight mg per serving and above represent levels at which the presence of ephedrine alkaloids in a dietary supplement may render the product injurious to health and presents a significant and unreasonable risk. FDA cannot say that it is a safe level, nor has

[1] FDA has limited information on which ingredients dietary supplement manufacturers are likely to substitute for ephedrine alkaloids. Given this uncertainty, FDA cannot comment on the safety of potential substitutes. FDA notes that manufacturers bear the burden of ensuring that any ingredients that they may substitute for sources of ephedrine alkaloids meet all safety standards for dietary supplements.

it been arrived at in a way that factored in some margin of safety. The evidence does not exist to establish a safe level. FDA notes that many members of the Food Advisory Committee stated that they were unaware of a basis for determining a safe level (Ref. 25). Thus, the agency is concerned about the potential for risk at levels below 8 mg per serving for individuals who are particularly sensitive to the effects of ephedrine alkaloids, or whose sensitivity could be increased through chronic use of these products or other processes (e.g., physical exercise).

Given the seriousness of the public health concerns and the uncertainty surrounding the risks attendant upon consumption of ephedrine alkaloids below 8 mg per serving, the agency solicits comments, and asks that they include data, particularly clinical data, on the safety of the use of less than 8 mg of ephedrine alkaloids per serving in dietary supplements. Should data and information become available that demonstrate that the use of less than 8 mg of ephedrine alkaloids per serving in dietary supplements poses a hazard to the public health, or that the level of ephedrine alkaloids that will render a product adulterated is higher than 8 mg per serving, the agency will consider modifying § 111.100 accordingly.

At this time, the agency is not proposing a level at which ephedrine, as opposed to the mixture of ephedrine alkaloids found in products containing botanicals, may render a product adulterated, even though some members of FDA's Working Group and of the Food Advisory Committee recommended that the agency establish a separate level for ephedrine (Refs. 25 and 27). There is some reason to believe that ephedrine may be particularly significant in contributing to the occurrence of many of the cardiovascular effects seen in the reports of adverse events because ephedrine is often the predominant alkaloid in botanical sources. In addition, ephedrine is known to exhibit more intense cardiovascular effects relative to the other ephedrine alkaloids (Refs. 5 and 9 through 13). For example, serious adverse events have been reported with the use of dietary supplements containing less than 5 mg ephedrine. However, the available data are difficult to interpret because of the uncertainties about the potentially interactive effects of the other ephedrine alkaloids in the raw botanical or botanical extract and the presence of other physiologically and pharmacologically active ingredients in the dietary supplement products that may act to potentiate the overall NS and CVS stimulatory effects of ephedrine and thus exacerbate the adverse effect. The agency requests comments on whether a separate dietary ingredient limit should be established for ephedrine in addition to ephedrine alkaloids, and if so, what that limit should be.

2. Proposed Compliance Procedures

In proposed § 111.100(a)(2), the agency states that it will use the high performance liquid chromatography (HPLC) method as specified in LIB No. 4053 to determine the level of ephedrine alkaloids in a dietary supplement. The agency developed this HPLC analytical method to identify and quantify ephedrine alkaloids from botanical sources. It was necessary for the agency to develop an analytical method because the official analytical methods used for the determination of ephedrine alkaloids in pharmaceutical dosage forms are unsuitable for botanical products. Current official analytical methods do not discriminate between ephedrine alkaloids and other alkaloids that may be in the botanicals (e.g., ephedroxane and methylbenzylamine) (Ref. 157). This HPLC method has made possible the resolution and quantification of the several different ephedrine alkaloids known to occur in the *Ephedras* and other botanicals, including ephedrine, pseudoephedrine, norephedrine, methylephedrine, methylpsuedoephedrine, norpseudoephedrine, and related alkaloids. This method is currently undergoing collaborative evaluation and testing.

FDA strongly recommends that manufacturers also use this or other methods that the agency adopts, although manufacturers will be free to use any alternative method that they find appropriate. However, FDA will use whatever method it adopts in this proceeding as the basis for its enforcement actions, and this method will be the legally established method. Therefore, manufacturers would be advised to compare their method of choice to the HPLC method to ensure that the alternative method produces similar results.

3. Proposed Limit for Ephedrine Alkaloids: Frequency and Per Total Daily Intake Basis

In addition to proposing a level for ephedrine alkaloids in dietary supplements at or above which their presence will render the product adulterated, the agency is proposing to address its concern that products containing ephedrine alkaloids below the dietary ingredient limit may be used in a manner that increases the likelihood, frequency, and severity of adverse events. Intake of multiple servings of ephedrine alkaloid-containing dietary supplements, particularly when such intake occurs within a relatively short timeframe (e.g., hours or within a day), can result in an excessive level of ephedrine alkaloids in the body that will increase the likelihood of an acute adverse event and the severity of the event that occurs. Concern over the hazards of taking several servings of ephedrine alkaloid-containing dietary supplements in a short period of time led several members of the Working Group and of the Food Advisory Committee to recommend that FDA limit the intake of dietary supplements containing ephedrine alkaloids to no more than four to five times per day and establish daily use limits, e.g., the amount of ephedrine alkaloids the consumer should not exceed in a day. In light of this, FDA evaluated the risks associated with different patterns of daily intake of ephedrine alkaloid-containing dietary supplements.

The average plasma half-lives for pharmaceutical ephedrine, pseudoephedrine, and phenylpropanolamine are approximately 6 hours (range 3 to 11 hours), 6 hours, and 4 hours, respectively (Refs. 10 through 12, 20, and 46). Generally, this means that after one half-life (e.g., 4 to 6 hours) half of the ephedrine alkaloids still remain in the blood. More than 24 hours are needed for complete clearance of a single serving of ephedrine alkaloids from the body. Because ephedrine alkaloids remain in the body for hours, when additional servings of an ephedrine alkaloid-containing dietary supplement are consumed, the ingested alkaloids are additive to those already in the body. This process will result in an increase in blood and tissue concentrations of ephedrine alkaloids. Generally, the higher the blood and other body tissue levels of ephedrine alkaloids, the greater the likelihood and severity of adverse events (Ref. 46).

Given the pharmacological evidence that average plasma half-lives of ephedrine alkaloids are approximately 4 to 6 hours, elevated blood levels of ephedrine alkaloids will be maintained if a serving is consumed every 4 to 6 hours. Because ephedrine alkaloids are stimulant substances, they can cause insomnia if taken close to sleeping hours. Thus, if 6 to 8 hours in a day are typically used for sleeping, there is a period of 16 to 18 hours per day in which consumers of ephedrine-containing dietary supplements would

have interest in consuming this substance. By dividing the 16 to 18 waking hours in a day by the largest average half-life for ephedrine alkaloids (i.e., 6 hours), the results reveal the possibility of taking a maximum of three servings per day.

Three servings of a dietary supplement that contains the proposed maximum per serving amount of ephedrine alkaloids (less than 8 mg) would yield a daily intake level of less than 24 mg ephedrine alkaloids. Thus, a dietary supplement product that contains ephedrine alkaloids and whose label or labeling instructs consumers to take 24 mg or more per day would present a significant and unreasonable risk of injury and illness under the conditions of use suggested or recommended in the labeling and thus would render the product adulterated under section 402(f)(1)(A) of the act. Similarly, an ephedrine alkaloid-containing product whose label or labeling instructs consumers to take 8 mg or more during a 6-hour period would instruct consumers to consume an amount of ephedrine alkaloids that has been shown to cause injury. This labeling also would present a significant and unreasonable risk and render the product adulterated under section 402(f)(1)(A) of the act.

FDA tentatively concludes that without a daily use limit, the per serving limit cannot be effective in reducing the potential for adverse events because consumers may unknowingly consume an excessive amount of ephedrine alkaloids by taking several servings of dietary supplements in a relatively short period of time. Therefore, FDA is proposing in § 111.100(b) that the labeling of dietary supplements that contain ephedrine alkaloids shall not suggest or recommend conditions of use that would result in intake of 8 mg or more ephedrine alkaloids within a 6-hour period or a total daily intake of 24 mg or more of ephedrine alkaloids. FDA is proposing this regulation under sections 402(f)(1)(A) and 701(a) of the act to ensure that ephedrine alkaloid-containing dietary supplements do not bear directions for use that will create a significant and unreasonable risk.

In some cases, the label directions for use of dietary supplements containing ephedrine alkaloids can cause consumers to exceed the per serving limit or to consume servings more frequently than every 6 hours. For example, FDA would consider the following label instructions to increase the risk of adverse events: ''take what your body needs'' or ''take 1 tablet (containing 7 mg ephedrine alkaloids) per serving, not to exceed 3 tablets per day.'' In the later example, the consumer may believe that it is safe to consume 3 tablets (21 mg ephedrine alkaloids) at one serving or servings separated by less than 6 hours. Examples where the agency would not consider that the directions for use would cause consumers to exceed the per serving limit or take serving more frequently than every 6 hours include ''take 1 tablet per day,'' ''take 1 tablet every 6 hours, do not take more than 3 tablets per day,'' or ''take 1 tablet not more than every 8 hours, do not take more than 2 tablets per day.''

4. Proposed Limitation on Duration of Use

The available data suggest that some types of adverse events may be related to the duration of using ephedrine alkaloids. Long-term use of sympathomimetic agents, such as ephedrine alkaloids, even at relatively low levels, is related to serious adverse events, including cardiomyopathy (i.e., disease of the heart muscle) and myocardial necrosis (death of heart cells and tissue), that can result in death (Refs. 7, 16, 49, 51, and 52). The scientific literature establishes that use of ephedrine alkaloids for a period of several months or years can result in cardiomyopathy (Refs. 66 through 68). Similarly, fatal cardiomyopathies have been seen in the AER's associated with chronic use of ephedrine alkaloid-containing dietary supplements at serving levels close to the dietary ingredient limit the agency proposed above (ARMS No. 11134 in Refs. 29 and 149a).

Concern about these types of adverse events with the long-term use of ephedrine alkaloids led several members of the Working Group (Ref. 27) and of the Food Advisory Committee (Ref. 25) to recommend that, in conjunction with a per serving dietary ingredient limit, FDA require a statement on the label of ephedrine alkaloid-containing dietary supplements to warn consumers not to use the product for a period longer than 7 days. These members stated that a 7-day use limit is standard guidance for the use of pharmacoactive drug substances, including ephedrine alkaloids, and may reduce the occurrence of adverse events related to long-term use of ephedrine alkaloids (Ref. 25). Moreover, a 7-day limit on the use of ephedrine alkaloids is supported by the AER's data, which show that over 60 percent of the adverse events occurred when ephedrine alkaloid-containing dietary supplements were used for more than 7 days.

For these reasons, FDA tentatively concludes that ephedrine alkaloid-containing dietary supplements that do not bear the statement ''Do not use this product for more than 7 days'' present a significant and unreasonable risk of injury and illness under the recommended or suggested conditions of use. Therefore, under sections 402(f)(1)(A) and 701(a) of the act, to reduce the potential for adverse events occurring as a result of consumers using ephedrine alkaloids for more than a period of 7 days, FDA is proposing to require in § 111.100(c) that the label of dietary supplements that contain ephedrine alkaloids state ''Do not use this product for more than 7 days.''

The agency notes that this warning focuses on duration of use, not on when reinstitution of use of ephedrine alkaloids is appropriate. FDA is not aware of definitive data on whether there is a period of time when the reinstitution of use of ephedrine alkaloids will not present a risk of adverse events. FDA solicits comments, particularly data, on this matter. In addition, FDA solicits comments on how consumers will interpret this label statement in terms of reintroducing dietary supplements containing ephedrine alkaloids in their diets.

5. Proposed Prohibition of Ingredients With Stimulant Effects

As previously discussed, because the nature and patterns of adverse events observed in the AER's were consistent with the known physiological and pharmacological effects of the ephedrine alkaloids, the agency focused its evaluation on the ephedrine alkaloids. However, the majority of the adverse events that have been reported to FDA have involved the use of dietary supplements that contain ephedrine alkaloids in combination with other ingredients, some with known physiological or pharmacological effects, including kola nut, yohimbe, willow bark, senna, and Uva ursi (Ref. 164). In many cases, the AER's showed that more severe adverse effects (e.g., heart attack, stroke, seizure) occurred with the use of dietary supplements that contained ephedrine alkaloids at levels below 20 mg together with other ingredients than were noted in the scientific literature with the use of ephedrine at 20 mg (Ref. 149a). These observations suggest that the other ingredients may act, in combination with the ephedrine alkaloids, to produce more frequent, more severe, or potentially different patterns of adverse effects than those noted with the use of an ephedrine alkaloid alone.

Moreover, the clinically significant adverse events that occurred with amounts of ephedrine alkaloids below the 8 mg per serving limit may have been related to the compounding effects of ephedrine alkaloids in combination with other ingredients. Because of the known additive effects that occur when ephedrine alkaloids are combined with certain types of other ingredients, such as stimulants, proposed § 111.100(a)(1), by itself, will likely not be effective in reducing the potential for adverse events. Certain types of other substances interact with the ephedrine alkaloids to increase the effects of the ephedrine alkaloids, thereby acting like more ephedrine alkaloids were contained in the product.

For example, caffeine is a nervous system stimulant that can induce nervousness, insomnia, and tachycardia (increased heart rate) (Refs. 7, 165, and 166). Intake of toxic levels of caffeine can cause death resulting from CV stimulatory effects (Ref. 46). Various botanicals are known to be sources of caffeine, including green tea, guarana, yerba mate (also known as *Ilex paraguariensis*), and kola nut (Refs. 167 through 172).

The scientific literature reveals that the frequency and severity of adverse effects increase when ephedrine alkaloids and caffeine are combined (Refs. 22, 73, 105, and 106). Recent clinical trials have focused on whether a combination of ephedrine and caffeine would be more effective in the treatment of obesity than ephedrine alone. The usual dosage of ephedrine and caffeine was 20 mg and 200 mg, respectively, given three times a day before meals. The results of these trials, certain of which were carefully designed and conducted to eliminate potential confounders to the interpretation of study results (e.g., concurrent medication usage, underlying diseases and conditions or other risk factors), indicate that the effects, including adverse effects, of combining ephedrine and caffeine are synergistic (Refs. 105, 173, and 174).

Caffeine and ephedrine also appear to be synergistic in thermogenesis, i.e., they increase the rate of thermogenesis by influencing different parts of the metabolic pathways (Refs. 173 and 175). While the resulting effects of combining ephedrine and caffeine could have a potentially positive impact on thermogenesis because of their effects on metabolic pathways, it may also account for increased adverse effects seen with combinations of these agents because of increased sympathetic stimulation of other organ-systems (e.g., CVS and NS). The synergistic adverse effects include an increased frequency of certain signs and symptoms, e.g., increased heart rate, insomnia, nervousness, and increased blood pressure, that are considered characteristic of sympathomimetic stimulation.

Other substances with stimulant effects in combination with ephedrine alkaloids may act to increase the likelihood of an adverse event. Yohimbine from the botanical yohimbe, in small doses, is reported to stimulate part of the nervous system and to cause elevated blood pressure, increased heart rate, tremor, and anxiety (Refs. 176 through 178). Because of their stimulant effects on the nervous system, combining sources of yohimbine with the ephedrine alkaloids may increase the likelihood, frequency, and severity of adverse events.

Therefore, the agency tentatively concludes that, based on the available evidence, adverse events may be related to the interactive or additive effects of stimulant substances in combination with ephedrine alkaloids in dietary supplements. This tentative conclusion is supported by statements made by several members of the Food Advisory Committee at the August 27 and 28, 1996, meeting (Ref. 25). For these reasons, the agency tentatively concludes that any dietary supplement that contains ephedrine alkaloids in combination with ingredients that produce the aforementioned effects presents a significant or unreasonable risk of injury or illness under the conditions of use suggested in the labeling or under ordinary conditions of use and are adulterated. To eliminate this risk, under sections 402(f)(1)(A) and 701(a) of the act, FDA is proposing § 111.100(d), which states that no ingredient, or ingredient that contains a substance, that has a known stimulant effect (e.g., sources of caffeine, yohimbine) may be included in a dietary supplement that contains ephedrine alkaloids.

The agency is aware that several manufacturers and distributors of ephedrine alkaloid-containing dietary supplements also market caffeine-containing dietary supplements that are intended to be used with a ''companion'' ephedrine alkaloid-containing dietary supplement. The caffeine-containing dietary supplements are often promoted as ''boosters'' or ''enhancers'' for the ephedrine alkaloid-containing product. Under these conditions of use, both the caffeine-containing and the ephedrine alkaloid-containing dietary supplement products present a significant and unreasonable risk of illness and injury under their labeled conditions of use and consequently are adulterated under section 402(f)(1)(A) of the act.

The agency is concerned that many of the dietary supplements implicated in the AER's contained substances that are known to have physiological or pharmacological effects that could increase the risk of adverse events when taken in combination with ephedrine alkaloids. For example, substances that reduce renal clearance interfere with the elimination of ephedrine alkaloids from the body by the kidneys (i.e., renal excretion) (Refs. 180 and 181) and thus may increase the risk of adverse effects when consumed in combination with ephedrine alkaloids. These substances include salicin, which is found in the botanical commonly known as willow bark, and amino acids in high concentrations (Refs. 181 and 182). By reducing renal clearance, higher levels of ephedrine alkaloids are maintained in the blood for longer periods of time, thus prolonging the effects of ephedrine alkaloids. The maintenance of high blood levels of ephedrine alkaloids increases the likelihood of adverse events, particularly in those who may be sensitive to the effects of ephedrine alkaloids. In addition, consumers may experience adverse events if more ephedrine alkaloids are consumed while blood levels are maintained because the absorption of additional ephedrine alkaloids into the bloodstream will result in even higher blood and tissue concentrations of ephedrine alkaloids and in any effects that may follow. Generally, the higher the blood levels of ephedrine alkaloids, the greater the risk of adverse events and the greater the likelihood that the adverse effects that do occur will be severe (Ref. 46).

Diuretics and laxative substances in an ephedrine-alkaloid-containing dietary supplement may also increase the likelihood, frequency, and severity of adverse events (Refs. 182 through 186). Uva ursi is a botanical diuretic contained in many ephedrine alkaloid products (Ref. 184). The compounds ursolic acid and isoquercetin found in Uva ursi are mild diuretics. The ephedrine alkaloids also exhibit diuretic effects (Ref. 4). For example, ephedrine has a mild diuretic effect, and pseudoephedrine has a marked diuretic effect. The use of a product that contains ephedrine alkaloids in combination with other substances with diuretic effects increases the likelihood and severity of consequent fluid and electrolyte imbalances, both of which could affect CVS and NS risks.

Senna and Cascara are examples of botanicals that contain potent stimulant laxative substances called

anthraquinone glucosides (Refs. 185 through 187). Use of excessive amounts of stimulant laxatives can cause stomach cramps, nausea, vomiting, and diarrhea. Chronic use may lead to laxative dependence, diarrhea, and, in severe cases, dehydration and electrolyte disorders (Ref. 188). Ephedrine is known to influence cellular potassium (an electrolyte) concentrations (Refs. 53 and 54). Use of laxative substances in combination with ephedrine alkaloids may act to increase the likelihood, frequency, and severity of adverse events. The agency requests comments, particularly data, on the interactive effects of other ingredients and the ephedrine alkaloids in dietary supplements. Based on the comments and data received by FDA, the agency may prohibit the use of ingredients that produce the aforementioned effects in a dietary supplement that contain ephedrine alkaloids.

6. Proposed Prohibitions on Claims

As described previously in section II.C.1. of this document, FDA has received numerous reports of adverse events associated with ephedrine alkaloid-containing dietary supplements promoted for use for weight loss, increased energy, body building, enhanced athletic performance, increased mental concentration, and enhanced well-being and with products promoted to be used as an alternative to illicit street drugs. While many of the products that were associated with adverse events contained more than one type of claim or representation on their label or in their labeling, the majority of adverse events reported to FDA are related to the use of products promoted or used for weight loss or energy purposes. Although fewer of the AER's were associated with products promoted for body building and enhanced well-being, clinically serious adverse events, including seizure, heart attack, and death, have been reported to FDA that were associated with the use of products represented for these purposes. At least one death in a young man has been reported with the use of a product promoted as an alternative to an illicit street drug.

In reviewing the AER's, it was evident that specific types of claims contained in the labeling of dietary supplements containing ephedrine alkaloids promoted different patterns of use. Claims such as weight loss and body building encouraged long-term use to achieve the product's purported effect (Ref. 189). In addition, claims of increased energy, increased mental concentration, or enhanced well-being, in a number of cases, encouraged short-term excessive consumption to achieve more of the product's purported effect (Ref. 190). Finally, the agency found that claims that suggest that the product is intended to be used as a substitute for an illicit street drug fostered abuse. Because claims in product labeling may influence how a consumer uses the product, claims in product labeling are a condition of use for dietary supplements.

Several Food Advisory Committee members identified a number of significant risks attendant to using dietary supplements containing ephedrine alkaloids for purposes such as weight loss, energy, or as an illicit street drug alternative, including adverse events that are associated with long-term use, excessive consumption, and abuse of ephedrine alkaloids (Ref. 25). Because the identified types of claims promote use patterns that are associated with adverse events, the agency has tentatively concluded that claim restrictions are necessary to maintain the integrity of the limit on the level of ephedrine alkaloids in dietary supplements that it is proposing in § 111.100(a)(1) and of the other proposed restrictions on the conditions of use of these dietary supplements.

a. *Claims that promote long-term use.* Claims in the labeling of dietary supplements that use of a product may result in effects such as weight loss or body building promote long-term use of the product because these effects cannot be achieved in a short period of time. Weight loss occurs when caloric intake is reduced or energy expenditure (e.g., exercise) is increased. To lose 1 pound (lb), approximately 3,500 kilocalories (kcal) must be expended by reducing caloric intake or by increasing energy expenditures (e.g., physical activity) or both (Ref. 191). Rapid weight loss is associated with health risks, including increased protein loss from the body stores and increased risk of gallstone formation (Ref. 27). In fasting, over 50 percent of rapid weight reduction is attributable to the loss of body fluids. Risks associated with rapid loss of fluids from the body include hypotension (i.e., reduction in blood pressure) and electrolyte disturbances. Steady weight loss over a longer period of time results in a true weight loss with a reduction of fat stores (Ref. 193). Guidelines recommend that a safe rate of weight loss is ½ to 1 lb per week (Ref. 194). Therefore, depending upon the amount of weight loss that the individual desires to achieve, weight loss programs may extend from weeks to months (Ref. 195).

Long-term weight loss practices have been documented in the scientific literature. A survey of weight control practices among 1,431 adults indicated that the average respondent participating in the survey had a weight loss attempt lasting from 5 to 6 months and had averaged one attempt a year for the past 2 years (Ref. 196). In addition, approximately 30 percent of persons trying to lose weight were chronic dieters and had been on weight loss plans at least 1 year (Ref. 196). Thus, this survey indicates that common weight loss practices can be characterized as long-term in duration and recurrent in nature.

Conversely, body building involves the building of lean muscle mass by strength and endurance training. The addition of muscle mass can be accomplished only through regular muscle work (weight training or similar conditions) coupled with a caloric increase (Ref. 197). To increase size and strength, a muscle must be exercised at 60 to 80 percent of its capacity several times a week. In addition, a gain of 1 lb of muscle requires about 2,500 extra calories, in addition to the calories needed for the training (Ref. 197). An increase of 700 to 1,000 calories (cal) to the daily diet should support a gain of 1 to 2 lb of lean muscle in 7 days (Ref. 197). Body building systems that include intensive physical training programs, controlled diet, and dietary supplementation purport to achieve results in 6 weeks (Ref. 198), and the individual must continue a training program to maintain or increase the muscle mass.

As previously mentioned in section III.C.4. of this document, long-term use of ephedrine alkaloids, even at relatively low levels, is related to serious adverse events, including cardiomyopathy (i.e., disease of the heart muscle) and myocardial necrosis (death of heart cells and tissue), that can result in death. After reviewing the scientific literature and the AER's as well as recommendations by the Working Group and by the Food Advisory Committee, FDA has tentatively concluded that ephedrine alkaloid-containing dietary supplements must bear the statement ''Do not use this product for more than 7 days,'' and that those that do not present a significant and unreasonable risk of injury and illness under the recommended or suggested conditions of use.

Significant and safe results from weight loss or body building should not and cannot be achieved within a period of 7 days. An individual could lose approximately 4 lb of body fat in 7 days under complete fasting conditions if the normal energy requirements are 2,000 cal per day. (This assumption is based

on the fact that 3,500 kcal must be expended to achieve 1 lb of weight loss.) As discussed above, however, this rate of weight loss is not safe or recommended.

Regarding body building, lean muscle mass cannot be built in 7 days (Ref. 197). Moreover, the scientific literature evidences that the use of ephedrine alkaloids during intense physical activity, such as body building, increases the risks of serious adverse events. Use of ephedrine alkaloids during periods of intense physical activity results in enhanced or synergistic actions on the sympathetic nervous system. It is through such enhanced physiological processes that chronic effects on the heart, such as myocardial necrosis (i.e., death of heart cells and tissue), can occur with prolonged use of ephedrine alkaloids (Refs. 16 and 197a).

Because safe and significant weight loss and body building cannot be achieved in a 7-day period, claims that promote these uses promote long-term use of ephedrine alkaloid-containing dietary supplements, which has been associated with serious adverse events. For this reason, FDA tentatively concludes that any claims that promote long-term use of ephedrine alkaloid dietary supplements, such as those for weight loss and body building, promote conditions of use that present a significant and unreasonable risk of illness and injury. Therefore, under sections 402(f)(1)(A) and 701(a) of the act, the agency is proposing in § 111.100(e) to prohibit dietary supplements that contain ephedrine alkaloids from being represented, either expressly or implicitly, for use for long-term effects such as weight loss or body building.

b. *Claims that promote short-term excessive consumption.* Many claims found on the labels of, or in the labeling for, ephedrine alkaloid-containing dietary supplements, including increased energy, increased mental concentration, and enhanced well-being, encourage the consumer to take more of the product than is indicated on the label to achieve more of the purported effect. Several members of the Food Advisory Committee stated that when a product is promoted to increase these types of effects, the claim encourages the consumer to exceed the labeled directions for use to gain more of the desired effects (Ref. 25). For example, if a product is promoted for energy, the consumer is encouraged to take more to gain greater energy.

Many of the AER's received by the agency were associated with dietary supplements containing ephedrine alkaloids that were promoted for one or more of these purposes. In a number of instances, the consumer took more than directed on the product label and experienced an adverse event (Ref. 190). Claims that promote excessive consumption, even for one or a very limited number of uses, are inconsistent with proposed § 111.100 (a)(1) and (b), because they encourage the consumer to take more than directed in the conditions of use set out on the label so that the consumer can achieve the purported effect.

In section II.C.2.a. and II.C.2.b. of this document, FDA described data from the clinical literature and AER's that show that consumption of an excessive amount of ephedrine alkaloids in a relatively short period of time is associated with serious adverse events, including seizure, psychosis, mania, heart attack, and death. The agency tentatively concludes that the potential for these serious adverse events to occur with excessive consumption of ephedrine alkaloids is a material fact with respect to consequences that may result from the use of a dietary supplement promoted for short-term effects that encourage excessive consumption, and therefore a material fact that must be disclosed on the label.

FDA's authority to require disclosure statements in the labeling of dietary supplement products derives from sections 201(n), 403(a)(1), and 701(a) of the act. Section 201(n) of the act states, ''If an article (e.g., a food or dietary supplement product) is alleged to be misbranded because the labeling or advertising is misleading, then in determining whether the labeling or advertising is misleading there shall be taken into account (among other things) not only representations made or suggested by statement, word, design, device, or any combination thereof, but also the extent to which the labeling or advertising fails to reveal facts material in light of such representations or material with respect to consequences that may result from the use of the article to which the labeling or advertising thereof or under such conditions of use prescribed in the labeling or advertising thereof or under such conditions of use as are customary or usual.'' Under section 403(a)(1) of the act, a food is misbranded if its labeling is false or misleading in any particular. Thus, the omission of a material fact from the label or labeling would misbrand a product. These statutory provisions, combined with section 701(a) of the act, authorize FDA to issue a regulation designed to ensure that persons using ephedrine alkaloid-containing dietary supplements will receive information that is material with respect to consequences that may result from the use of the supplement under its labeled conditions.

Therefore, FDA is proposing in § 111.100(f)(1) that the label or labeling for dietary supplements that contain ephedrine alkaloids that purport to be or are represented, either expressly or implicitly, to be used for short-term effects, such as increased energy, increased mental concentration, or enhanced well-being, must state ''Taking more than the recommended serving may cause heart attack, stroke, seizure, or death.'' However, given the significance and the potentially life-threatening nature of the adverse events that may occur when individuals consume excessive amounts of ephedrine alkaloids, the agency requests comments on whether this statement should appear on the label of dietary supplements containing ephedrine alkaloids, regardless of any claims appearing on the label or in labeling.

FDA wants to provide an approach to placement of this information that will give it a prominence that will ensure that it will be read and understood by consumers but that will result in its presentation only once on the label panel or on each page of the labeling. Because the consequences of excessive use of ephedrine alkaloids can be serious, the agency tentatively concludes that this information should be on the same label panel or on the same page of the labeling (i.e., the same field of vision) as the claim. However, FDA is proposing to provide for the use of one disclaimer on the label panel or on each page of labeling in situations in which multiple claims appear on the label panel or page of labeling where repetitive presentation of the disclaimer could be burdensome. FDA tentatively concludes that where the label panel or page of labeling contains multiple claims, and the relationship between each of those statements and the disclaimer can be made obvious, the disclaimer need only appear once on each label panel or in each page of labeling.

FDA experience has been that one of the most effective ways of tying two label statements that are physically separate on the same panel is through the use of a symbol such as an asterisk. Symbols have been used within nutrition labeling since its inception in 1973 and have proven to be an effective way of relating labeling information to explanatory footnotes. For example, asterisks have been used adjacent to names of vitamins and minerals present at very low levels to refer the consumer to a footnote stating ''Contains less than

2 percent of the Daily Value (formerly the U.S. Recommended Daily Allowance).'' FDA is unaware of any data indicating consumer difficulties with such use of symbols. The use of symbols would also help differentiate between the label statements to which the disclaimer is referring and the other label claims to which the disclaimer does not apply (e.g., authorized health claims or nutrient content claims).

The agency points out that the proposed requirements for the disclaimer also extend to labeling: There are potentially many vehicles (e.g., placards, pamphlets, catalogs, books) that would have to bear the disclaimer. The agency is concerned that the disclaimer be prominent in these forms of labeling. Even with the flexibility of the use of an asterisk to tie the claim and the disclaimer to a single claim, the disclaimer could be obscured in pages of text of a package insert, pamphlet, or book if it did not appear on the same page or panel (i.e., in the same field of vision) as the claim itself. Because of the variety of possibilities for the presentation of the disclaimer, the agency tentatively concludes that for labeling, as for labels, it is important that the disclaimer appear within the same field of vision, that is, on each package panel or page where a claim is made.

Section 403(f) of the act requires mandatory label or labeling information to be prominently placed on the label with such conspicuousness (compared with other words, statements, designs, or devices, in the labeling) as to render it likely to be read and understood by the ordinary individual under customary conditions of use. In other instances where information must appear in a prominent and conspicuous manner on the product label, FDA has proposed that the information be ''in easily legible print or type in distinct contrast to other printed or graphic matter'' (e.g., § 101.13(d)(2)). Therefore, to be consistent with previous actions and to ensure that the information is presented in a way that makes it likely to be read, FDA tentatively concludes that the information be presented in easily legible print or type in distinct contrast to other printed or graphic matter.

FDA has long held that accompanying information should be in a size reasonably related to that of the information it modifies (e.g., §§ 101.22(i)(2) and 102.5(b)(2)(ii)). More recently, this relative prominence has been expressed as a size no less than that required by § 101.105(i) for the net quantity of contents statement, except where the size of the claim is less than two times the required size of the net quantity of contents statement, in which case the accompanying information can be no less than one-half the type size of the information modified, but no smaller than one-sixteenth of an inch (see e.g., § 101.13(g) (1) and (i)(2)). The agency also has long held that one-sixteenth of an inch is the minimum type size for disclaimer statements, unless the package complies with § 101.2(c)(5) (see e.g., § 101.13(g)(1) and (i)(2)). One-sixteenth of an inch is specified in § 101.2(c) as the minimum type size for most other mandatory information on the principal display panel or information panel, e.g., designation of ingredients, name and place of business, and quantitative information for relative claims. Consequently, the agency tentatively concludes that the minimum type size for such information should be one-sixteenth of an inch.

Accordingly, FDA is proposing to provide for the disclaimer, as outlined above, in § 111.100(f)(2). If FDA adopts § 111.100(f)(2), the labeling of a dietary supplement that contains ephedrine alkaloids and that purports to be, or that is represented as, useful for short-term effects, such as increased energy, increased mental concentration, or enhanced well-being, would be misleading, and thus misbranded, if it does not include the disclaimer set out in § 111.100(f)(1).

The agency recognizes that most of the claims that will require the use of the disclaimer, if this proposal is adopted, will be statements that are made subject to section 403(r)(6) of the act. That provision also requires that a disclaimer accompany the statements. In the **Federal Register** of December 28, 1995 (60 FR 67176), FDA proposed requirements for the disclaimer that is required to accompany statements made under section 403(r)(6) of the act. FDA requests comments on how best to place the disclaimer proposed in this document in conjunction with the disclaimer required under section 403(r)(6) of the act on the label or in labeling of dietary supplements so that both disclaimers will be read and understood by consumers.

c. *Claims that suggest that the product is intended to be used as a substitute for an illicit street drug.* FDA is aware that some ephedrine alkaloid-containing products are being promoted as alternatives or substitutes for such illicit street drugs as MDMA (4-methyl-2, dimethoxyamphetamine), a methamphetamine analogue. MDMA is also known as ''ecstasy,'' ''XTC,'' and ''X.'' The precursor of MDMA is MDA (3,4 methylene dioxyamphetamine), an amphetamine whose use results in destruction of serotonin-producing neurons that play a direct role in regulating aggression, mood, sexual activity, and tolerance to pain (Ref. 16). Many products claiming to be herbal alternatives to MDMA bear claims on their label or in the labeling that highlight these mood-or mind-altering effects.

Such street drug alternative claims do not fall within the scope of the claims that Congress intended to permit on the labels or in the labeling of dietary supplements. The Dietary Supplement Health and Education Act of 1994 (the DSHEA) added section 201(ff) to the act (21 U.S.C. 321(ff)), which provides, in part, that the term dietary supplement means a product ''intended to supplement the diet'' that bears or contains one or more dietary ingredients. While Congress did not elaborate in the legislative history on what it intended the phrase ''intended to supplement the diet'' to mean, many of the congressional findings set forth in the DSHEA suggest that Congress intended dietary supplements to augment the diet to promote health and reduce the risk of disease.

In using the term ''diet'' in section 201(ff) of the act, Congress did not define this term in either the act or the legislative history. The term ''diet'' is defined in Webster's Dictionary as ''an organism's usual food and drink'' (Ref. 200). Dorland's Medical Dictionary defines ''diet'' as ''the customary allowance of food and drink taken by any person from day-to-day, particularly one especially planned to meet specific requirements of the individual, and including or excluding certain items of food'' (Ref. 201). These definitions suggest that the diet is composed of usual food and drink that may be designed to meet specific nutritional requirements. Under section 201(ff) of the act, dietary supplements are food except for purposes of section 201(g) of the act and thus may be part of, or augment, the diet. These common sense definitions for the term ''diet'' do not encompass alternatives to illicit street drugs.

Products promoted to be an alternative to or substitute for an illicit street drug are intended to be used for recreational purposes to effect psychological states (e.g., to ''get high'' or to promote feelings of euphoria). Illicit street drugs are not food or drink and thus, cannot supplement the diet. In addition, use of products claiming to be alternatives to illicit street drugs does not promote health or reduce the risk of disease, the intended use for dietary supplements suggested in the

congressional findings listed in the DSHEA. In fact, serious adverse events, including cardiac arrhythmia that resulted in death, are associated with the use and abuse of products promoted for use as an alternative to MDMA (see ARMS No. 10862 in Ref. 149a).

Because alternatives to illicit street drugs are not intended to be used to supplement the diet, products that purport to be or that are represented, either expressly or implicitly, for use as an alternative to a street drug are not dietary supplements within the meaning of section 201(ff) of the act. Therefore, manufacturers, packers, and distributors cannot take advantage of the exemption for structure function claims from the drug definition in section 403(r)(6) of the act. Because these products are intended to be used to affect the structure and function of the body, they are drugs within the meaning of section 201(g)(1)(C) of the act.

7. Warning Label Statements

Several members of the Working Group and of the Food Advisory Committee recommended that specific information be conveyed in a warning or cautionary statement for ephedrine alkaloid-containing dietary supplements (Refs. 25 and 27). Persons having certain diseases or taking specific medications known to interact with ephedrine alkaloids are at risk of suffering adverse events with the use of dietary supplements containing ephedrine alkaloids. Generally, use of ephedrine alkaloids at any intake level by these persons is contraindicated (Refs. 10 through 12, and 55). For these persons, a warning label statement can be a useful means of alerting them to potential consequences that can result from the use of the product. Table 5 identifies groups that are at risk if they use ephedrine alkaloids. In addition, many consumers who are unaware that they are sensitive to the effects of ephedrine alkaloids may not recognize the significance of early warning signs and symptoms as potential indicators of more serious side effects (e.g., dizziness or severe headache may be early symptoms of hypertension or stroke). Under these circumstances, a warning statement could provide information on what actions the consumer should take if certain symptoms occur.

FDA has received several AER's, some clinically significant, that were associated with the use of dietary supplements containing ephedrine alkaloids at levels below the level proposed in § 111.100(a)(1) where signs and symptoms including high blood pressure, chest pain, increased heart rate, severe headache, and nausea were observed (Ref. 149a). Although these AER's are not sufficient to support a lower per serving limit, they do provide cause for concern for lower per serving levels. To reduce the potential for adverse events to occur at these lower per serving levels, FDA tentatively concludes that a warning statement on the labels of dietary supplements containing ephedrine alkaloids is necessary, in conjunction with dietary ingredient limitations and other requirements proposed in this document, to protect the public health.

FDA is therefore proposing in § 111.100(g) to require that a specific warning statement appear on the labels of dietary supplements containing ephedrine alkaloids. FDA's authority to require label warning statements on dietary supplement products derives from sections 201(n), 403(a)(1), and 701(a) of the act. These statutory provisions authorize FDA to issue a regulation designed to ensure that persons using dietary supplements will receive information that is material with respect to consequences that may result from the use of a product under its labeled conditions.

a. *Caution statement suggested by industry.* Several dietary supplement industry trade groups met with FDA on November 30, 1995, and suggested that dietary supplements containing ephedrine alkaloids bear a specific warning statement (Ref. 199). Representatives from the National Nutritional Foods Association (NNFA), the American Herbal Products Association (AHPA), the Nonprescription Drug Manufacturers Association (NDMA), and the Utah Natural Products Alliance (UNPA) (hereinafter referred to as the dietary supplement industry [2]) recommended the following statement:

CAUTION: Taking more than the recommended amount will not necessarily increase benefits. Begin use with one-half or less the recommended dose to assess your tolerance. (If Pertinent) Please note: This product contains caffeine and should not be taken by those wishing to eliminate caffeine from their diet. Seek advice from a health care practitioner if you are pregnant or nursing or if you are at risk or are being treated for high blood pressure, heart, thyroid or psychiatric disease, diabetes, depression, seizure disorder, stroke or difficulty in urination due to prostate enlargement. Consult your health care professional before use if you are taking an MAO inhibitor or any other prescription drug. Discontinue use and consult your health care professional if dizziness, nausea, sleeplessness, tremors, nervousness, headache, heart palpitations or tingling sensations occur. **NOT INTENDED FOR SALE TO OR USE BY PERSONS UNDER THE AGE OF 18. KEEP OUT OF REACH OF CHILDREN. DO NOT EXCEED RECOMMENDED DOSE.**

FDA has carefully considered proposing adoption of the statement suggested by industry. While the agency considers the industry suggestion to be a good starting point, FDA tentatively concludes that some changes are necessary in the statement if it is to fulfill its purpose of fairly warning consumers about the special risks attendant to use of dietary supplements that contain ephedrine alkaloids.

b. *Tentative conclusions.* The dietary supplement industry suggested that the warning statement begin with the term ''caution.'' FDA, however, questions whether this term is adequate to convey the severity of the harm that can result from the use of the product. Because use of ephedrine alkaloid-containing dietary supplements has the potential to cause serious injury to certain subgroups of the population, the agency tentatively concludes that the use of the term ''WARNING'' is warranted. The term ''WARNING'' is commonly used to denote danger, and, therefore, the use of this term will communicate to consumers the harm that could result to the special populations that are the subject of the warning.

The dietary supplement industry suggested that the statement include the instruction ''Seek advice from a health care provider if you are pregnant or nursing or if you are at risk or are being treated for high blood pressure, heart or thyroid disease, diabetes, difficulty in urination due to prostate enlargement.'' Several members of the Working Group and of the Food Advisory Committee recommended that a warning statement direct consumers who have certain diseases or conditions that increase the risk of adverse events not to use the product or to see a health care provider prior to using the product (Refs. 25 and 27). The feeling of these members was that a health care provider could assess the potential risks for the individual consumer if he or she uses the product.

FDA concurs with this portion of the industry's labeling recommendation. As discussed in section II.C. of this document, based on the scientific literature and the known physiological and pharmacologic effects of ephedrine alkaloids, an individual who is pregnant or nursing, has high blood pressure, heart or thyroid disease, or difficulty in

[2] FDA is using this shorthand for convenience. It does not intend to imply that these groups represent the entire dietary supplement industry.

urination because of prostate enlargement has an increased risk for experiencing serious adverse effects with the use of ephedrine alkaloids. However, FDA also tentatively finds that the warning statement should be broadened to address other individuals who may place themselves at particular risk if they consume the product. The relevant scientific literature, case reports and AER's suggest that persons suffering from depression or other psychiatric conditions, glaucoma, or seizure disorders are also at increased risk of experiencing an adverse event if they consume ephedrine alkaloid-containing products.

Use of ephedrine alkaloids during pregnancy or while nursing can cause adverse effects in the fetus or the infant. Ephedrine alkaloids can cross the placental wall and can be absorbed by the fetus when taken by a pregnant woman (Refs. 10 through 12 and 55). Similarly, ephedrine is excreted in the breast milk and can be consumed by the nursing infant. The fetus, infants, and children are sensitive to the effects of ephedrine alkaloids and thus are more likely to experience adverse events (Refs. 39 and 41).

Use of ephedrine alkaloids by persons with high blood pressure can result in blood pressure elevations or loss of adequate medical control of hypertension (Ref. 64) which increases the risk of serious consequences (e.g., stroke and heart attack) (Refs. 62 and 70). Because ephedrine alkaloids also interfere with the regulation of serum potassium levels (Refs. 53 through 55), individuals with heart disease who use ephedrine alkaloids are at greater risk of cardiac dysrhythmias (i.e., abnormal heart rhythms) (Refs. 18 and 56), myocardial ischemia (i.e., inadequate circulation of blood and oxygen to the heart muscle), and infarction (i.e., death or damage of heart cells, also called heart attack) (Refs. 57 through 61).

With respect to thyroid disease, individuals with hyperthyroidism (resulting from increased secretion of thyroid hormone) show increased sensitivity to adrenergic agents, such as ephedrine alkaloids, which can result in thyroid storm with dire consequences (e.g., cardiac dysrhythmias, congestive heart failure, coma, and death) (Refs. 39, 41, 55, and 202).

For persons with diabetes, use of sympathomimetics can result in an increase in blood sugar and loss of diabetic control (Refs. 29, 41, and 51). In addition, ephedrine can cause constriction of the urinary bladder sphincter and ultimately lead to dysuria (increased, painful, or difficulty in urination). This condition is not only associated with prostate enlargement or only seen in men. Published case reports and AER's received by the agency document the finding that urinary retention following the use of ephedrine alkaloid-containing products can occur in both females and males, including young boys without any history of prostate enlargement (see ARMS No. 10298 and 11164 in Ref. 149a and Refs. 102, 103, 123, and 124).

Use of ephedrine alkaloids by persons suffering from depression or other psychiatric conditions increases the risk for the occurrence of serious adverse events, including psychosis and mania (Refs. 81 through 96, 98, 99, 109, and 220). Because ephedrine can cause an increase in intraocular pressure (i.e., pressure inside the eyeball), use of ephedrine alkaloids by persons with glaucoma will worsen this disease, which over time, can result in blindness (Refs. 39 and 41). Finally, persons with seizure disorders who use ephedrine alkaloids have an increased risk for experiencing a seizure (Refs. 63, 65, and 80). Because the nature of the risks associated with the use of ephedrine alkaloids for persons who have the diseases and health-related conditions listed above, it is important that these consumers be advised to consult a health care provider before using ephedrine alkaloid-containing dietary supplements.

With regard to the statement in industry's suggested statement ''if you are at risk or are being treated for high blood pressure * * *,'' the agency considers it unlikely that consumers will be able to adequately evaluate their risk for developing the conditions listed in this statement. Most of these conditions are not self-diagnoseable. In addition, individuals who have a disease or condition listed in this statement, but who are not currently being treated, may believe that they are not at risk of experiencing an adverse event. Consequently, the agency tentatively concludes that the warning statement needs to include an instruction to consult a health care provider before using an ephedrine alkaloid-containing dietary supplement.

The dietary supplement industry statement only instructs the consumer to consult his or her health care professional before use if he or she is taking an MAOI or any other prescription drug. FDA tentatively concludes that this statement should be broader because of the need for professional help in assessing the risks of ephedrine alkaloid intake with a range of conditions.

However, people using MAOI drugs should not use ephedrine alkaloid-containing products at all. Several members of the Working Group and of the Food Advisory Committee recommended that the warning statement advise consumers not to use the dietary supplements containing ephedrine alkaloids if they are taking these types of drugs (Refs. 25 and 27). Because the use of MAOI drugs in combination with ephedrine alkaloids results in blood pressure elevations and increases the risk of serious consequences (e.g., stroke and heart attack), FDA is proposing to warn against use of ephedrine alkaloid-containing products in this circumstance (Refs. 10 through 12, 39, 41, and 55). Because persons remain at risk while the MAOI drug remains in the body, FDA tentatively concludes that consumers need to be informed that it may take up to 2 weeks for the MAOI drug to clear the body (Refs. 203 and 204).

Because MAOI drugs increase the effects of sympathomimetic agents, and consequently will increase the frequency and severity of adverse effects, persons taking such drugs should be given as much information as possible. The agency is concerned that some patients may not be fully informed about MAOI drugs, may not fully understand or remember all the information given to them, or with the passage of time, may forget or lose information that has been provided. Thus, the warning statement needs to be as informative as possible.

Rather than include general language, such as ''any prescription drug'' in the warning statement, FDA tentatively finds that it is important to identify specific types of prescription and OTC drugs that contain ingredients that in combination with ephedrine alkaloids are known or expected to increase the likelihood, frequency, or severity of adverse effects. Therefore, FDA tentatively concludes that consumers need to be warned not to use ephedrine alkaloid-containing dietary supplement in combination with specific drugs, such as drugs for depression, psychiatric or emotional conditions (Refs. 10 through 12, 55, and 205); drugs for Parkinson's disease (Ref. 55); methyldopa (Ref. 206); or any product containing ephedrine, pseudoephedrine, or phenylpropanolamine (ingredients often found in allergy, asthma, cough/cold and weight control products) (Refs. 180 and 207 through 209).

FDA tentatively finds that the drug methyldopa needs to be identified on the label. It increases the pressor results of sympathomimetic agents, such as ephedrine alkaloids, resulting in hypertension (Ref. 206). FDA has

reached a similar tentative judgment with respect to ephedrine, pseudoephedrine, and phenylpropanolamine because each of these substances, in combination with an ephedrine alkaloid-containing dietary supplement, could lead to an additive effect and consequently increase the risk of serious adverse events. While many consumers may not be familiar with the term ''ephedrine,'' ''pseudoephedrine,'' or ''phenylpropanolamine,'' they may be aware of the type of product being taken for a specific condition or ailment, e.g., allergy, asthma, cough/cold, and weight control products.

The agency recognizes that because of the large number of drugs for depression, psychiatric or emotional conditions, and Parkinson's disease that are contraindicated for use with ephedrine alkaloids and the limited amount of space on the labels of dietary supplements, not all of them can be listed on the label. However, the conditions for which the consumer is taking the drug can be identified, using less label space. If consumers are unsure whether their drug may interact with the ephedrine alkaloids, they should be cautioned to check with their health care professional before using the dietary supplement.

The dietary supplement industry suggested that the statement include the instruction ''Discontinue use and consult your health care professional if dizziness, nausea, sleeplessness, tremors, nervousness, headache, heart palpitations or tingling sensations occur.'' Several members of the Working Group and of the Food Advisory Committee also recommended that any warning statement include information on what actions the consumer should take if certain symptoms occur (Refs. 25 and 27).

Signs and symptoms, such as dizziness, severe headache, rapid or irregular heart beat, chest pain, shortness of breath, nausea, sleeplessness, noticeable changes in behavior, or loss of consciousness are often early warning signs of serious illness or injury, including heart attack, stroke, or seizure. It is important that the consumer stop using the product if these signs or symptoms occur because continued use of the product may aggravate the adverse effects. The agency tentatively finds that the terms ''stop'' and ''call'' should be used for ''discontinue'' and ''consult,'' respectively, because they are more simple and direct terms.

The proposed warning statement instructs the consumer to call a health care professional if any of the listed symptoms occur. A health care professional will be able to evaluate the significance of the signs and symptoms, determine the risks of more serious adverse events occurring, and prescribe any treatment that may be necessary. The effects, such as tremor, sleeplessness, and tingling sensations, that are included in the instruction suggested by the industry are not usually clinically serious and will likely cease once the product use is discontinued (Refs. 210). For these reasons, FDA tentatively concludes that the statement needs to include the instruction to ''Stop use and call a health care professional immediately if dizziness, severe headache, rapid or irregular heart beat, chest pain, shortness of breath, nausea, noticeable changes in behavior, or loss of consciousness occur.''

The dietary supplement industry suggested that the statement include a direction for the consumer not to exceed the recommended dose. Members of the Working Group and of the Food Advisory Committee recommended that the warning statement include a direction for the consumer not to exceed the recommended serving or dose (Refs. 25 and 27).

The agency concurs with the industry's suggestion. FDA tentatively finds that this type of statement is necessary to provide information instructing the user not to consume the product excessively. Excessive consumption of ephedrine alkaloids is associated with adverse events, including heart attack, stroke, seizure, and death. Therefore, the statement is a material fact about the consequences of use of the product. However, FDA has used the term ''serving'' rather than ''dose,'' because the agency considers the term ''serving'' to be more appropriate for use on a food label.

The dietary supplement industry suggested that the statement include the instruction that ''Taking more than the recommended amount will not necessarily increase benefits.'' Similarly, the Working Group suggested that the warning statement contain the instruction that ''Larger quantities may not be more effective.'' The agency is not aware of any data or other information that establishes that there are benefits from the use of dietary supplements containing ephedrine alkaloids. Therefore, the agency would be concerned about requiring a statement on the label that implies a judgment (that the product has benefits) that the agency has not made. While some questions can be raised in this regard under section 403(r)(6) of the act, the agency considers them to be moot because the instruction for the consumer not to exceed the recommended serving eliminates the need for the ''Taking more than recommended * * *'' statement.

The dietary supplement industry suggested that the statement advise the consumer to: ''Begin use with one-half or less the recommended dose to assess your tolerance.'' The agency addressed limiting the levels of ephedrine alkaloids contained in dietary supplements in proposed § 111.100 (a)(1) and (b). In addition, because of label space constraints, the agency is trying to keep the warning statement as short as possible. Therefore, FDA tentatively concludes that there is no reason to require inclusion of this information.

The dietary supplement industry recommended the following in a caution statement, if appropriate for the product: ''This product contains caffeine and should not be taken by those wishing to eliminate caffeine from their diet.'' The Food Advisory Committee also suggested that other stimulants with their source, such as caffeine from Kola nut, be identified on the label of a dietary supplement containing ephedrine alkaloids. However, the agency is proposing to prohibit stimulant substances in combination with ephedrine alkaloids in dietary supplements. Therefore, FDA tentatively concludes that there is no reason to require the inclusion of such a statement.

The dietary supplement industry recommended that the direction ''Not for use by persons under the age of 18'' be included in the warning statement. Several members of the Working Group and of the Food Advisory Committee suggested that the warning statement include a direction that the product is not intended for use by persons under the age of 18. The agency has received limited reports of adolescents abusing or misusing ephedrine alkaloid-containing dietary supplements. Moreover, the agency has stated elsewhere in this document that claims implying usefulness of these products as alternatives to illicit street drugs render the product an unauthorized drug. FDA considers that removal of alternative street drug claims from the labeling of dietary supplements will significantly reduce or eliminate the appeal of these products to adolescents and therefore is not proposing to require that this direction be included in the warning. However, the agency requests comments on whether the direction ''not for persons under the age of 18'' should be included.

The industry group's statement included the instruction ''Keep out of reach of children.'' Children show increased sensitivity to the effects of sympathomimetic agents compared to adults (Refs. 39 and 41) and are, therefore, at increased risk for experiencing adverse events from the use of ephedrine alkaloids. The agency has limited data and information that dietary supplements containing ephedrine alkaloids are being given to, or are associated with accidental overdosage by, children. FDA requests comment, particularly data, on whether this statement is necessary to alert consumers to the fact that ephedrine alkaloid-containing dietary supplements should not be made available to children.

c. *The agency's proposal.* Based on FDA's authority under sections 201(n), 403(a)(1), and 701(a) of the act, the agency proposes to require manufacturers to include the warning statement set out in § 111.100(g)(1) in the labeling of their ephedrine alkaloid-containing products. The agency tentatively finds that the warning statement is necessary to disclose material facts about the consequences of using the product, and that it will help to reduce the risk that some individuals will experience an adverse event from using this type of product.

The agency solicits comments on all aspects of the warning statement, including data to support any specific instruction. The agency also solicits comments on approaches to shorten or simplify the warning statement. Because substances contained in ingredients (e.g., ephedrine alkaloids contained in *Ephedra*) are not required to be listed in the ingredient list on the label of dietary supplements, the agency is concerned that consumers and health care providers may not be aware that ephedrine alkaloids are contained in the product and thus may not necessarily recognize the seriousness of the symptoms listed in the statement, when they occur. FDA requests comments on whether the warning statement should disclose that ephedrine alkaloids are contained in the product. In addition, the agency is concerned that some AER's suggest that a pattern of starting and stopping use of dietary supplements containing ephedrine alkaloids may increase an individual's susceptibility to experiencing adverse events. FDA requests comments on whether the warning statement should disclose the possibility of increasing the risk of adverse events by a pattern of stopping and starting use. Based on the comments received by FDA, the warning statement proposed below may need to be modified.

In an effort to promote uniformity in labeling, FDA is proposing to require that the warning statement appear on the labels of ephedrine alkaloid-containing dietary supplements in the exact manner presented in proposed § 111.100(g)(1), except when the disclaimer proposed in § 111.100(f) appears on the same label panel as the warning statement, in which case the instruction ''Do not exceed recommended serving'' would not have to appear in the warning statement. However, the agency recognizes that other ingredients that may be used in ephedrine alkaloid-containing dietary supplements may have consequences of use that need to be disclosed on the label. The agency requests comments on how to allow for warning statements for other ingredients in conjunction with the ephedrine alkaloid warning statement on the label of dietary supplements. In addition, the agency solicits comments on the format of the warning statement to improve its clarity (e.g., should the statement be set out in bullets).

d. *Placement of warning statement on label.* The agency intends to provide an approach to the placement of the warning label statement to give manufacturers flexibility to design their own label warning formats, while ensuring that consumers are given adequate notice of the information contained in the warning.

Section 403(f) of the act requires that information appearing on the label or labeling be prominently placed and appear with such conspicuousness (as compared with other words, statements, designs, or devices, in the labeling) as to render it likely to be read by the ordinary individual under customary conditions of use. In the agency's rulemaking that mandated warning statements on certain protein products, the agency decided not to mandate specific requirements for type size and other format elements. However, the agency did require that the warning statement appear ''prominently and conspicuously on the principal display panel of the package label'' (§ 101.17). In addressing the placement of the label warning, the agency noted that the seriousness and nature of the risks associated with the use of protein products in very low calorie diets was sufficient to require placement of the warning statement on the principal display panel (§ 101.17).

FDA tentatively concludes that the warning statement that it is proposing must appear prominently and conspicuously on the label of dietary supplements containing ephedrine alkaloids so that consumers are given adequate notice of the information contained in the warning. While the risks associated with the use of dietary supplements containing ephedrine alkaloids are serious, the agency is not proposing to require that the warning label statement for dietary supplements containing ephedrine alkaloids appear on the principal display panel. The agency recognizes that, because of the length of the required warning statement, in many cases it may be impracticable for the warning statement to appear on the principal display panel without interfering with the placement of other information that is required to appear on that panel.

The requirement in the act for prominent display means that the warning statement must be presented on the label or labeling in a manner that renders it as readily observable and likely to be read. In this regard, the agency's experience with the graphic requirements for the new nutrition label has been that a box around required label information greatly increases the prominence of the information placed inside the box. Moreover, focus group discussions regarding warning labels show that messages put in a boxed area help consumers to distinguish the message from other information as well as draw attention to it (Ref. 210a). Therefore, FDA is proposing to require in § 111.100(g)(3) that the warning statement for ephedrine alkaloid-containing dietary supplements be separated from other information by a box. If FDA adopts these regulations, manufacturers will have the flexibility to design their own label and warning label format subject to § 111.100(g)(3).

Section 201(k) of the act defines the term ''label'' as ''a display of written, printed, or graphic matter upon the immediate container of any article'' and further states a requirement that ''any word, statement, or other information appear on the label shall not be considered to be complied with unless such word, statement, or other information also appears on the outside container or wrapper, if any there be, of the retail package of such article * * *.'' Thus, if FDA adopts its proposal to require that a warning statement appear on the label of ephedrine alkaloid-containing dietary supplements, the warning statement would also have to appear on the retail package of such a product, if that package is not the immediate container.

FDA requests comments on these proposed requirements for placement of the warning statement.

In addition to this proposed regulation, the agency has issued proposed and final rules on dietary supplements, including premarket notification procedures for new dietary ingredients (61 FR 50774, September 27, 1996) and label warning statements and unit dose packaging requirements for iron containing dietary supplements (62 FR 2218, January 15, 1997). The agency has proposed to codify each of the proposed and final regulations in different parts of the Code of Federal Regulations. The agency believes that it would be easier for consumers as well as for the dietary supplement industry to find and use regulations for dietary supplements if they were consolidated into one part of the CFR. Accordingly, FDA is proposing to revise part 111 to consolidate the regulations for dietary supplements. FDA is proposing to change the title of part 111 from ''Current Good Manufacturing Practice for Dietary Supplements'' to ''Dietary Supplements.'' This is necessary to reflect that other regulations for dietary supplements in addition to regulations for current good manufacturing practice will be contained in this part. FDA is proposing to establish four subparts in part 111: Subpart A—General Provisions, Subpart B—Current Good Manufacturing Practice for Dietary Supplements, Subpart C—New Dietary Ingredients, and Subpart D—Restricted Dietary Ingredients. The labeling provisions for dietary supplements will continue to be placed in 21 CFR part 101.

D. Other Approaches Considered by the Agency

In choosing the proposed approach to limit the risks presented by ephedrine alkaloids in dietary supplements, the agency considered, but rejected, several other approaches. Because the act does not allow premarket review authority for dietary supplements, FDA has no data and information to establish conditions of use that will ensure the safe use of ephedrine alkaloid-containing dietary supplements. Therefore, the only viable approach available to FDA is one in which the agency prohibits levels of a substance in, or conditions of use for, a dietary supplement that it can prove may render the product injurious to health or that present a significant or unreasonable risk of illness and injury under the conditions of use suggested or recommended in the labeling or under ordinary conditions of use.

The agency is unaware of any classical toxicological studies whose results identify ''no adverse effect levels'' for ephedrine alkaloids directly applicable to humans, or whose results establish intake-response curves for ephedrine alkaloids in dietary supplements and that could be used to establish a level of ephedrine alkaloids that are safe for consumers to use in dietary supplements. The intake-response relationships between ephedrine alkaloids and their effects in humans are unknown for both botanical sources and marketed dietary supplement products containing ephedrine alkaloids. Moreover, because there are consumers who may be sensitive to the effects of ephedrine alkaloids because of a variety of factors that are not readily identifiable or predictable, a margin of safety based on classical toxicological principles likely cannot be determined. For these reasons, the agency tentatively finds that the use of a classical toxicological approach to determine a safe level of ephedrine alkaloids in dietary supplements is not a usable approach.

Several members of the Food Advisory Committee recommended that FDA consider the risk associated with the use of dietary supplements containing ephedrine alkaloids in the context of any benefit that the consumer may receive from the use of these products (Ref. 25). In applying a risk-to-benefit calculation, a certain amount of risk may be accepted if there is a meaningful benefit to be gained by the consumer (Ref. 25). However, the Food Advisory Committee members were unable to identify a benefit for ephedrine alkaloids in terms of supplementing the diet (Ref. 25). Moreover, risk-benefit analysis is something that is done under the act for drugs, not food.

Several members of the Working Group suggested that any limitations on the level of ephedrine alkaloids in dietary supplements be based on the use of pharmaceutical ephedrine in OTC oral bronchodilator drugs and the use of *Ephedra* in traditional herbal medicine (Ref. 27). Other members of the Working Group and several members of the Food Advisory Committee found difficulty in extrapolating from OTC drug data because the products, the populations using the products, and intended use of the products are dissimilar (Ref. 25). In addition, the latter members were concerned about the potential for adverse events to occur, particularly in populations sensitive to the effects of ephedrine alkaloids, if therapeutic levels of ephedrine are used in dietary supplements (Ref. 25). Several members of the Food Advisory Committee were also concerned about using data from the use of *Ephedra* in traditional herbal therapies to support the safety of the use of ephedrine alkaloids in dietary supplements because the therapeutic use of ephedrine alkaloids has traditionally not involved the same conditions, the same populations, or the same purposes as those under which dietary supplements are used (Ref. 25).

The agency considered the applicability of OTC drug data and tentatively concluded that these data, which involve use in a restricted population (physician-diagnosed mild asthmatics) under limited directions for use (i.e., not to exceed 12.5 to 25 mg every 4 hours, not to exceed 150 mg in 24 hours) and with warnings and contraindications for use, has no application here. The determination of safety for drugs is based on a weighing of the proven benefits of the use of the product against the risks. This approach may not be used with foods under section 402(a) of the act. The only question for food use under this section is whether it will cause harm or not. While the concept of ''unreasonable risk'' as stated in section 402(f)(1)(A) of the act, may imply that some evaluation of effects, including risks and benefits, is appropriate for dietary supplements, it is not necessary to reach that question here, because, as stated above, there are no demonstrated benefits for ephedrine alkaloids. Moreover, the risks attendant on consuming dietary supplements containing levels of ephedrine permitted in oral bronchodilator drugs (12.5 to 25 mg ephedrine per dose) are manifest.

In addition, there is no basis for extrapolating from data from a subgroup of the population, diagnosed asthmatics, who may be less sensitive to the effects of ephedrine (Ref. 25) than the general population, to the general population, among which a significant number of people are known or suspected of being very sensitive to ephedrine.

Finally, the agency finds it inappropriate to extrapolate data from the use of OTC ephedrine-containing drugs because dietary supplements contain a mixture of several ephedrine alkaloids and a variety of other ingredients, including vitamins, minerals, other botanicals, and other physiological and pharmacologically active substances, while OTC drugs contain only a single ephedrine alkaloid. The presence of other alkaloids and substances in dietary supplements may act to increase the likelihood, frequency, and severity of adverse events from the use of these products. In fact, clinical studies show that adverse events are more likely to occur when ephedrine is combined with other substances, such as caffeine. Therefore, the fact that pharmaceutical ephedrine

has been approved by FDA for an OTC use does not provide assurance of safety for the use of ephedrine alkaloids in dietary supplements.

The agency considered the applicability of traditional use of botanical sources of ephedrine alkaloids in establishing dietary ingredient levels for ephedrine alkaloids in dietary supplements. A history of long usage of a medicinal herb in traditional therapies does not provide an assurance of safety for a component of a dietary supplement because these conditions of use are so different. The history of use of *Ephedra* in traditional Asian medicine primarily for the treatment or relief of respiratory symptoms provides insufficient assurance that ephedrine alkaloids will not present a significant or an unreasonable risk of injury to consumers who use dietary supplement products containing ephedrine alkaloids to supplement the diet. Not only are dietary supplements marketed for different uses than the traditional use of *Ephedra*, most dietary supplements are marketed in a form that is different than the form in which it has been traditionally used, e.g., as a concentrated extract in capsules and tablets, in the presence of other substances rather than the raw botanical in a tea.

FDA is not aware of any systematic collection of data related to adverse effects occurring in individuals treated with *Ephedra* in traditional medicine. However, several reference texts list precautions and contraindications for the use of the botanical *Ephedra* in traditional medicine preparations (Refs. 6, 14, and 146). Thus, FDA tentatively concludes that use of ephedrine alkaloids in traditional Asian medicine does not provide the basis on which to establish a safe level of use of ephedrine alkaloids in dietary supplements.

IV. Analysis of Impacts

FDA has examined the impacts of the proposed rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601–612). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select the regulatory approach that maximizes net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). Executive Order 12866 classifies a rule as significant if it meets any one of a number of specified conditions, including having an annual effect on the economy of $100 million or adversely affecting in a material way a sector of the economy, competition, or jobs, or if it raises novel legal or policy issues. If a rule has a significant economic impact on a substantial number of small entities, the Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize the economic impact of that rule on small entities.

FDA finds that this proposed rule is an economically significant rule as defined by Executive Order 12866, and finds under the Regulatory Flexibility Act that this proposed rule will have a significant impact on a substantial number of small entities. Finally, FDA, in conjunction with the Administrator of the Office of Information and Regulatory Affairs (OIRA) of the Office of Management and Budget (OMB), finds that this proposed rule is a major rule for the purposes of congressional review (Pub. L. 104–121).

A. Market Failure

The market failure addressed by this regulation is that some consumers may not have sufficient information on the health risks associated with dietary supplements containing ephedrine alkaloids to make informed choices concerning the consumption of these products, despite the presence of warning labels of various types on many of these products. Ordinarily, consumers would be expected to seek out and pay for the level of information they consider appropriate with respect to consumption decisions. However, the level of information currently utilized by consumers with respect to these products may be less than optimal because of consumer perceptions that products marketed as foods or derived from botanical sources are inherently safe, and the cost of generating evidence to evaluate the safety of these products may be quite high. In addition, the onset of the adverse health events associated with these products is frequently quite unexpected or occurs without identifiable risk factors, and consumers may have little or no opportunity to adapt their behavior based on experience with the risks of these products prior to suffering a severe adverse event.

B. Regulatory Options

FDA has the following primary options:

1. Take no action.
2. Take no regulatory action, but generate additional information on which to base a future regulatory action.
3. Take proposed action.
4. Take proposed action, but with a higher potency limit.
5. Ban dietary supplements that contain ephedrine alkaloids.
6. Take proposed action, but do not require warning statement.
7. Require warning statements only.

C. Benefits and Costs

1. Option 1—Take No Action

By convention, the option of taking no action is the baseline in comparison with which the costs and benefits of the other options are determined. Therefore, neither additional costs nor benefits are associated with taking no action. Although no regulatory costs or benefits are generated if no regulatory action is taken, preventable adverse events will continue to occur if no regulatory action is taken. The number of such adverse events is expected to increase over time because the marketplace for these types of products has been increasing rapidly since the 1994 passage of the DSHEA, and the number of AER's associated with use of these products has also been increasing sharply over the last few years (Figure 1).

2. Option 2—Take No Regulatory Action, but Generate Additional Information on Which To Base a Future Regulatory Action

FDA has the option of taking no regulatory action but generating additional information on which to base future regulatory action on this issue. The benefit of generating additional information is a reduction in the substantial uncertainty concerning the specific nature of the relationship of the adverse events associated with dietary supplements containing ephedrine alkaloids and, possibly, a more precisely targeted regulation. A more precisely targeted regulation could imply potency limits either higher or lower than the proposed potency limits, and either more or fewer ingredient and labeling restrictions than those proposed. The cost of generating additional information is the cost of whatever activity is undertaken to generate the additional information and the health cost of any adverse events to these products that would occur if regulatory action were delayed but that would not occur if regulatory action were not delayed.

3. Option 3—Take Proposed Action

a. *Benefits.* The benefit of the proposed action is a potential reduction in the number or severity of adverse events associated with dietary supplements containing ephedrine alkaloids. The proposed rule consists of the following four actions: (1) Per day and per serving potency limits on total ephedrine alkaloids (TEA), (2) restrictions on caffeine and other

stimulants, (3) mandatory warning statement, and (4) labeling restrictions.

To estimate the benefits of these actions, a percentage decrease in the current number of adverse events associated with dietary supplements containing ephedrine alkaloids will be estimated for each regulatory action listed above. The estimated effects of all proposed actions will then be combined to obtain a total reduction in the expected annual number of adverse events. This percentage reduction will then be applied to an estimate of the current number of such adverse events to obtain an estimated number of adverse events avoided per year. The estimate of the current number of adverse events will be based on, but not identical to, the current number of relevant AER's because of uncertainty over a number of issues including, for example, the degree to which the relevant adverse events are reported. These sources of uncertainty will be discussed in greater detail later.

Each of the proposed actions may affect the number of adverse events by reducing the number of people who consume the relevant products or by modifying their use of these products in a manner that reduces the risk of an adverse effect. In addition, the potency limits and ingredient restrictions may affect the number of adverse events by reducing the probability that those who consume these products will suffer an adverse event. Each of these effects will be considered in turn, beginning with the effect of the proposed actions on the number of people who consume these products.

The proposed potency limits and other ingredient restrictions may affect the number of people consuming these products because they may affect the value placed by consumers on the use of these products. Some information on the likely effect of the proposed potency limits on the consumption of these products comes from a report from one firm that marketed an ephedrine alkaloid-free substitute for a supplement that previously contained ephedrine alkaloids. The sales of the substitute product were reportedly approximately 33 percent lower than the sales of the ephedrine alkaloid-containing product (Ref. 211). In the absence of more specific information, it is reasonable to suppose that a given reduction in sales is associated with a proportionate reduction in the number of people consuming these products.

It would not be reasonable to suppose the proposed potency limits and other ingredient restrictions would have a greater effect on the sales of these products than complete elimination of all ephedrine alkaloids from these products. First, the functional effect, as perceived by consumers, of removing all ephedrine alkaloids from a product is probably greater than the perceived functional effect of removing some of the ephedrine alkaloids and removing some ingredients that interact with those ephedrine alkaloids. Second, if only some firms remove ephedrine alkaloids from their products, relatively close substitutes will exist for the prior formulations of those products because other firms might not remove ephedrine alkaloids from their products. However, if all firms make the same changes in their products, then relatively close substitutes will not exist for the prior formulations of those products. Therefore, the proposed potency limits and other ingredient restrictions are estimated to reduce the number of people consuming these products by between 0 to 33 percent. The effect of the potency limits on the probability of an adverse event for those who continue to consume these products will be addressed later in this section.

The proposed warning statement is also likely to reduce the number of people consuming these products because a few of the relevant products do not currently have warning statements, and because, in some cases, the proposed warning statement is more comprehensive, more focused, and more strongly worded than existing warning statements. The only information available on the effect of warning statements on sales concerns diet soft drinks containing saccharin. Following the introduction of warning statements relating to saccharin, annual sales of diet soft drinks containing saccharin were reported to be 15 percent below what they would otherwise have been (Ref. 212). The effect of the proposed warning statement for dietary supplements containing ephedrine alkaloids will probably be smaller than the effect of the saccharin warning label on diet soft drinks because most such supplements already have some type of warning statement. Therefore, the proposed warning statement will probably reduce the number of people consuming these products by 0 to 15 percent.

The proposed label claim restrictions are also likely to reduce the number of people consuming these products by making the marketing of these products more difficult. The only information available on the potential effects of label claims on sales concerns ready-to-eat breakfast cereals. Following an advertising campaign relating bran consumption to a reduced risk of developing cancer, sales of high bran breakfast cereals were reported to have increased approximately 40 percent (Ref. 213). The effect of eliminating label claims on dietary supplements containing ephedrine alkaloids will probably be smaller because the claims involved are more general, and because other sources of information on the purported effects of ephedrine alkaloids are readily available or have been used recently enough that consumers are familiar with them.

However, approximately 10 percent of the AER's involved supplements labeled as alternatives to street drugs. Assuming that consumers of these products will not purchase these products if they are not labeled as alternatives to street drugs, the labeling restriction will reduce expected adverse events by at least 10 percent. Therefore, the proposed restriction on label claims will probably reduce the number of people consuming these products by between 10 percent and 40 percent.

In addition to these consumption effects, the proposed potency limits and ingredient restrictions will probably also decrease the likelihood that those who continue to consume these products will suffer an adverse event.

FDA is not aware of clinical information, particularly evidence from well-designed and conducted human studies on the relationship between intakes of ephedrine alkaloids from botanicals and the probability of an adverse event. One method of approaching the estimation of the health benefits of reduced exposure to ephedrine alkaloids is to consider the proportion of adverse event reports that involve products with TEA levels greater than that allowed under the proposed potency limits. FDA was able to obtain information on the actual exposures associated with adverse events for 13 products that provided intakes of less than 20 mg TEA per reported use by multiplying the consumer's reported use level against an FDA product analysis result. These reports provided information on the lower end of the range of estimated intakes by consumers. Among these 13 reports of adverse events associated with intakes of less than 20 mg, 9 involved consumer intakes of between 8 mg and 20 mg/per serving. This approach suggests that the proposed potency limit might reduce the expected number of adverse events by at least 80 percent, although the actual reduction is probably higher because the 13 reports did not include the many adverse event reports that occurred at intakes above 20 mg TEA per serving. On the other hand, the actual reduction might also be lower because the 13 reports did not include

all adverse event reports that occurred at intakes below 20 mg TEA per serving.

This approach to estimating the impact of the proposed potency limits assumes that the probability of an adverse event is related to intakes of TEA. If the probability of an adverse event is not related to TEA intake, then the potency limits may result in little or no reduction in the expected number of adverse event reports. For example, if individual sensitivities to ephedrine alkaloids are the major underlying factor in the reported adverse events, then it is possible that there may be no ''safe'' intake for these persons. Based on this information, all that can be said concerning the proposed potency limits is that they may reduce the expected number of adverse events by between 0 to 80 percent.

The restriction on other stimulants, including caffeine, should also reduce the probability of an adverse event. Combinations of ephedrine alkaloids and caffeine, at sufficiently high doses, are associated with an increased probability of an adverse event. For example, one study found that 60 percent of the study subjects had an adverse reaction to a combination of 20 mg ephedrine and 200 mg caffeine, while only 44 percent had an adverse reaction to 20 mg ephedrine alone (Ref. 105). Thus, in this study, the presence of 200 mg caffeine appears to have increased the probability of an adverse event from consumption of 20 mg ephedrine by about 50 percent. Comparable information is not available on the effect of combinations of ephedrine and caffeine at lower levels of either ephedrine or caffeine. Similarly, no information is available on the effect of other stimulants or other ephedrine alkaloids.

An informal review of 217 adverse event reports featuring dietary supplements suspected of containing ephedrine alkaloids found that 99 reports featured products for which labeled ingredient information was available. Of those reports, 70 percent involved products labeled as containing a source of caffeine. The levels of caffeine and ephedrine alkaloids in these products is not known. Assuming that these adverse event reports are typical of all relevant adverse event reports and that 50 percent of the reported adverse events to products labeled as containing caffeine may have been due to the presence of caffeine in conjunction with ephedrine alkaloids, the restriction on stimulants is estimated to reduce the expected number of adverse events by up to 35 percent. However, the impact of the proposed stimulant restrictions may be somewhat lower because the impact may depend on the levels of stimulants and ephedrine alkaloids involved, and the levels of stimulants and ephedrine alkaloids found in dietary supplements may be lower than the levels used in the study on which this estimate is based. In order to address this possibility, the restrictions on stimulants will be assumed to reduce the expected number of adverse reactions by 25 percent.

In order to use the estimated risk reductions discussed above to derive an expected reduction in the number of adverse events, the current number of adverse events must be estimated. There are a number of issues involved in estimating the current number of adverse events based on the number of reported adverse events.

The first issue is that the data base of over 600 AER's includes all reports thought to be related to the consumption of ephedrine alkaloid-containing dietary supplements, even though the nature of the available evidence did not allow specific cause and effect determinations for the majority of individual reports. FDA, therefore, used additional information to provide assurance that the patterns of signs and symptoms associated with the ephedrine alkaloid-containing dietary supplements were likely due to the presence of ephedrine alkaloids in these products. One approach to addressing this issue is to examine the evidence for positive dechallenge and rechallenge when product use is discontinued and reinitiated, respectively. The relationship of the reported adverse events to the consumption of dietary supplements categorized as containing ephedrine alkaloids has been corroborated by dechallenge in about 27 percent of the AER's. Positive rechallenge was reported in about 4 percent of the AER's. The majority of AER's, however, lacked sufficient information to evaluate the presence or absence of dechallenge or rechallenge effects. Therefore, the number of cases in which dechallenge alone or in combination with rechallenge was tried but did not occur is not available; nor is there information on whether dechallenge and rechallenge would have occurred in the large number of reports which lack such information. It is possible that all cases might have been associated with positive dechallenge and rechallenge results if such information were available. On the other hand, a certain number of false reports might also be expected. The proportion of reported adverse events actually related to the consumption of dietary supplements suspected of containing ephedrine alkaloids is probably between 27 and 90 percent. Within this range, FDA believes the most likely value is around 80 percent and, therefore, tentatively assumes that 80 percent of the reported adverse events are actually related to the consumption of dietary supplements. FDA requests comments on this assumption.

The second issue is the uncertainty that all 600 AER's involved products that actually contained ephedrine alkaloids. Confirmation of the presence of ephedrine alkaloids in problem products is not available in all cases. The likelihood of the presence of ephedrine alkaloids is based on the labeling of the products involved, FDA's own market survey (including laboratory analysis of 125 marketed products), and the similarity of the reported adverse events to the known effects of ephedrine alkaloids. The proportion of reported adverse events associated with dietary supplements that involve supplements containing ephedrine alkaloids is probably between 25 and 90 percent. Within this range, FDA believes the most likely value is around 80 percent and, therefore, tentatively assumes that 80 percent of the reported adverse events associated with consumption of dietary supplements involve supplements that contain ephedrine. FDA requests comments on this assumption.

The third issue is that the actual number of adverse events is likely to differ from the reported number of adverse events because all adverse events are probably not reported. This issue is particularly important with respect to passive reporting systems that rely on the voluntary submission of data, such as the system used to gather the AER's relevant to this issue.

Typical reporting rates for passive reporting systems addressed to adverse events associated with drugs are generally assumed to be on the order of 10 percent. Reporting rates are higher than usual if the potential health risks associated with a particular substance are widely publicized, if the adverse events are considered to be otherwise unusual, and if reports are gathered from a variety of sources. On the other hand, reporting rates would be lower than usual if consumers and physicians assume that dietary supplements are incapable of producing adverse events because they are not drugs or because they are ''natural.'' In order to incorporate this uncertainty, the reporting rate for the relevant adverse events is assumed to be 10 percent.

Based on the current number of reported adverse events and the assumptions discussed above

concerning the relationship between the number of reported adverse events and the underlying number of adverse events, the expected annual number of adverse events involving these products is approximately 1,100 cases. Applying the risk reductions discussed previously for the proposed actions implies a reduction in the health risks from these products such that the expected number of adverse events involving these products will be reduced by between approximately 400 cases and 1,100 cases per year. Based on published estimates of the value consumers might place on reducing the risk of the general types of adverse events involved, these benefits are valued at between $240 million and $670 million per year (Ref. 215).

Table 6 summarizes these results. The first column is the type of adverse event. ''Serious CVS'' refers to serious cardiovascular system events, including myocardial infarctions, dysrhythmias, strokes, and cardiomyopathies. ''Serious NS'' refers to serious nervous system events, including seizures, loss of consciousness, vestibular events, and psychiatric events. ''Less clinically significant'' events may include certain types of dermatological events and gastrointestinal events. The second column is the average annual number of AER's from January 1993 to June 1996. Because the sales of these products is increasing rapidly, and the reports of adverse events are also increasing rapidly (see Figure 1), FDA believes that this is a conservative estimate of benefits. The 3-year average has been used rather than the growth trend because extrapolating short-term growth trends into the future can result in large errors. The third column is the estimated average annual number of adverse events over this time period based on what FDA believes are the most likely values for the relevant assumptions. The fourth column is the estimated reduction in adverse events from all proposed actions, given as a range from low to high. These estimated reductions are based on adding the effects of the proposed actions as summarized in Table 7. The low end of this range represents a 35 percent reduction in the estimated annual adverse events and the high end represents a 100 percent reduction. The estimates have been rounded to the nearest ten. The fifth column is the value of reducing the risk of particular adverse events such that one expected adverse event is avoided per year across the at-risk population, in thousands of dollars. The sixth column is the estimated value of the annual risk reductions for the various adverse events in millions of dollars, given as a range from low to high, rounded to the nearest million.

TABLE 6.—ESTIMATED VALUE OF ANNUAL RISK REDUCTION FROM PROPOSED ACTIONS

Type of event	Annual reported cases [1]	Estimated annual cases [2]	Reduction in estimated annual cases [3]	Value of estimated risk reduction per case ($ thousands) [4]	Value of estimated risk reduction ($ millions) [5]
Death	6	40	10–40	5,000	70–190
Serious CVS	27	170	60–170	837	50–140
Serious NS	29	190	70–190	1,483	100–280
Ab. liver function	7	50	20–50	3	0
Other serious	12	80	30–80	775	20–60
Less serious	93	600	210–600	0.4	0
Total	174	1,110	390–1,110	NA	240–670

[1] Annual reported cases are based on the average number of adverse event reports per year between January 1993 and June 1996. Trends in the data were not extrapolated because of the short timeframe involved.

[2] Estimated annual cases are based on the following assumptions: (1) 80 percent of the reported adverse events involving the consumption of dietary supplements suspected of containing ephedrine alkaloids are actually related to the consumption of dietary supplements, (2) 80 percent of the supplements involved in the reported adverse events that are related to the consumption of supplements actually contain ephedrine alkaloids, and (3) 10 percent of adverse events to the dietary supplements containing ephedrine alkaloids are reported. Thus, the estimated number of annual cases is $0.8 \times 0.8 \times 10$ times the number of annual reported cases. Considerable uncertainty exists with respect to the validity of the assumptions on which this estimate is based and the actual number of annual cases may be higher or lower than the estimate.

[3] The low end of the range of the reduction in estimated annual cases represents a 35 percent reduction in estimated annual cases. The high end of this range represents a 100 percent reduction in estimated annual cases. The 35 percent and 100 percent estimates are based on adding up the estimated effects of the proposed actions, as indicated in Table 7.

[4] The value of the risk reduction per case is based on published estimates of the value consumers place on reducing the risk of the general types of adverse events involved (Ref. 215).

[5] The value of the estimated risk reduction is based on multiplying the risk reduction per case times the reduction in the estimated annual cases.

TABLE 7.—COMBINED EFFECT OF PROPOSED ACTIONS

Proposed action	Estimated reduction in adverse events (in percent)
Actions reducing consumption of supplements containing ephedrine alkaloids:	
Potency limits and ingredient restrictions	0–33
Warning statement	0–15
Label claim restrictions	10–40
Combined effect	10–88
Actions reducing probability of adverse event given consumption:	
Potency limits	0–80
Ingredient restrictions	25
Combined effect	25–100

TABLE 7.—COMBINED EFFECT OF PROPOSED ACTIONS—Continued

Proposed action	Estimated reduction in adverse events (in percent)
Combined effect of all proposed actions	35–100

b. *Costs.* The primary social costs of the proposed actions are the compliance costs, which include the one-time costs associated with relabeling and reformulating the affected supplements and the recurring costs associated with testing for the level of ephedrine alkaloids in conjunction with future product reformulations or changes in ingredients, and the value of the utility losses to any consumers who do not value the reformulated supplements as highly as supplements currently found on the market. This cost must be considered somewhat paradoxical because the cause of this loss of value, the reduction or removal of ephedrine alkaloids, would also reduce or eliminate the risks associated with using these products. In addition, indirect social costs in the form of capital losses and temporary unemployment may arise from the distributive effects of the proposed action, which are discussed below. Some portion of the compliance costs will be borne by manufacturers and distributors of these products, and some portion will be passed on to consumers of these products. Costs borne by manufactures and distributors will be borne by the owners, stockholders, and employees of those firms.

In addition to the potential impact of compliance costs, manufacturers and distributors of the dietary supplements containing ephedrine alkaloids will be adversely affected by the reduction in consumption of these products caused by the proposed actions. Also, manufacturers, distributors, and importers of raw or bulk Ma huang and other affected ingredients may be affected by these consumption effects. These effects are distributive effects rather than social costs because they do not involve the loss of productive resources, and because a loss of business in one sector of the economy is generally associated with an increase in business in competing sectors. However, as indicated above, social costs may be involved to the extent that otherwise productive capital investment is lost and temporary unemployment is generated. In addition, distributive effects are obviously very significant to the affected parties.

FDA has previously estimated the cost of relabeling all dietary supplements in the economic impact analysis for the proposal on nutrition labeling of dietary supplements that was published in the **Federal Register** of December 28, 1995 (60 FR 67184) (the December 1995 proposal). Total discounted labeling costs based on an 18 month compliance period were estimated to be between $52 and $85 million. This cost included recurring testing or analytical costs based on testing the nutrient content of each product an average of once every 5 years. Based on comments to the December 1995 proposal, these estimates were revised in the economic impact analysis of the final rule. The revised estimate was $194 million, with $91 million of these costs occurring in the first 18 months and the remainder being a discounted sum of future analytical costs. In order to use this estimate as a basis for estimating labeling costs for the current proposal, the previous estimate must be adjusted to account for the compliance period associated with this rule and the fact that not all dietary supplements contain ephedrine alkaloids.

The proposed effective date of any regulation based on this proposal will be 180 days after the date of publication of the final rule. If the nutritional labeling rule had a compliance period of 180 days rather than 18 months, the total estimated labeling costs would have been $334 million, with $286 million of these costs occurring in the first 6 months.

Adjusting the previous estimate to account for the fact that not all dietary supplements contain ephedrine alkaloids requires information on the proportion of dietary supplements that contain ephedrine alkaloids. The market surveys identified 125 dietary supplements suspected of containing ephedrine alkaloids. A public comment submitted to the Special Working Group of the Food Advisory Committee suggested the number of such products is at least 200 (Ref. 216). In the December 1995 proposal, the total number of dietary supplement products was estimated to be between 4,000 and 25,000. In the final rule entitled ''Iron-Containing Supplements and Drugs: Label Warning Statements and Unit-Dose Packaging Requirements'' that published in the **Federal Register** of January 15, 1997 (62 FR 2218), this estimate was revised to 29,000. If 200 dietary supplements contain ephedrine alkaloids, then about 1 percent of the estimated total number of dietary supplements contain ephedrine alkaloids and the cost of changing the labels on dietary supplements containing ephedrine alkaloids would be about 1 percent of the costs estimated for changing the labels on all dietary supplements.

Another method of estimating the proportion of dietary supplements that contain ephedrine alkaloids is to use sales data. This method is complicated by the fact that sales might not be evenly distributed across dietary supplements, implying that the proportion of dietary supplement sales accounted for by supplements that contain ephedrine alkaloids may not be the same as the proportion of dietary supplement products that contain ephedrine alkaloids.

Ma huang and other ephedra products have been reported to represent 3.5 percent of individual botanical sales in selected health food stores, while individual sales of products containing single botanicals are estimated to make up about 53 percent of total botanical supplement use (Ref. 3). Information is not available on the proportion of products with multiple botanical ingredients that contain ephedrine alkaloids. Botanical supplement retail sales have been estimated to have accounted for approximately 26 percent of total dietary supplement retail sales in 1995 (Ref. 217). However, this estimate includes a number of product categories under dietary supplements that would not be considered dietary supplements under the legal definition of a dietary supplement. After adjusting for the definition of dietary supplements, supplements containing botanicals accounted for approximately 35 percent of dietary supplement retail sales in 1995. The definition of dietary supplement used in this estimate includes vitamins, minerals, and botanical (including herbal) supplements.

If all supplements containing ephedrine alkaloids are characterized as

botanical supplements, this information suggests that between 1 and 17 percent of dietary supplement use involves products that contain ephedrine alkaloids. If the proportion of dietary supplement products containing ephedrine alkaloids reflects the proportion of dietary supplement sales accounted for by products containing ephedrine alkaloids, then between 1 and 17 percent of the total number of dietary supplement products contain ephedrine alkaloids, or between 200 and 5,000 products.

Based on the preceding information, labeling costs for this proposal are estimated to be between 1 and 17 percent of the costs previously estimated for changing the labels on all dietary supplements, after adjusting those costs for the length of the compliance period. Thus, total discounted labeling costs for this proposal are estimated to be between $3 million and $60 million, with between approximately $3 million and $50 million of these costs occurring in the first year and between a minimal amount and approximately $0.5 million in every year after the first year.

If the proposed 180 day compliance period for making the proposed label changes coincided with some portion of the 18-month compliance period of the final rule requiring nutritional labeling of dietary supplements, then some portion of the combined labeling costs of the two regulations would be eliminated because some firms would be able to make both labeling changes during normally scheduled labeling changes. The degree of overlap of the compliance periods of these regulations depends on the date on which the final rule is published. If appropriate, this consideration will be addressed in the economic analyses of the final rule.

Information is not available on the cost of reformulating the affected products. Reformulation may simply involve reducing the amount of the ingredient source of the ephedrine alkaloids and removing the restricted ingredients. One method of approaching this issue is to consider the types of personnel and the amount of effort that might be required for reformulation. A reasonable assumption is that it might take a scientist from 1 to 4 weeks to develop an acceptable reformulation. In this case, the cost of reformulating a product would be between $1,000 and $5,000, based on median weekly earnings data for 1994 and 50 percent overhead (Ref. 218).

Many dietary supplements containing ephedrine alkaloids probably contain restricted ingredients or do not meet the proposed potency limits on TEA and will either have to be reformulated or removed from the market. The number of dietary supplements containing ephedrine alkaloids has been estimated, above, to be between 200 and 5,000. Under this assumption, if all products were reformulated, the one-time cost of reformulating the affected products would be between $0.2 million and $25 million. The recurring costs associated with testing for ephedrine alkaloid levels in conjunction with future product reformulations was addressed in the labeling costs.

Another cost associated with product reformulation is the cost of any inventory losses involving products produced prior to the publication of a final rule based on this proposal that cannot be sold by the date that final rule goes into effect. The proposed effective date of any final rule on this issue is 180 days after publication of the final rule. FDA has no information on the amount of inventory typically carried for these products, but tentatively assumes that 180 days will provide sufficient time to utilize existing stock.

In addition to the compliance costs discussed above, the proposed action will also lead to utility losses for some consumers because it removes products with certain characteristics from the marketplace. Theoretically, the value of this utility loss is the difference in the value consumers placed on the eliminated products and the value of the products purchased in place of the eliminated products. Estimating this loss requires estimating demand curves for the eliminated products and for the products substituted for the eliminated products.

Identifying likely substitutes for dietary supplements as currently formulated is complicated by the fact that a wide range of effects are attributed to these supplements, for example, energy, weight loss, body building, and increased mental concentration. However, little reliable information is available on the actual effects produced by these supplements. In addition, various other botanical substances exist that might be used in supplements to replace either some portion of the ephedrine alkaloids or the restricted ingredients and might produce effects that consumers may perceive to be similar to the effects that consumers attributed to these supplements as currently formulated. Finally, FDA has insufficient information to estimate demand curves for dietary supplements containing ephedrine alkaloids or potential substitutes for these products.

Based on these considerations, FDA cannot place bounds on the value of the consumer utility losses that may be associated with this action. However, if substitute products could be identified, then the absolute price difference between the affected products and the substitute products would represent a lower bound on consumer utility losses. No comparable argument is available for the upper bound of the utility loss.

In addition to compliance costs and utility losses, the proposed action will also generate distributive effects. The total reduction in the consumption of dietary supplements containing ephedrine alkaloids from all proposed actions including the potency limits, ingredient restrictions, labeling restrictions, and mandatory warning statement was estimated in the analysis of the benefits of this option to be between 10 percent and 33 percent. Total annual sales of supplements containing Ma huang have been estimated to be between $600 million and $700 million (Ref. 219). Therefore, sales of these products may be reduced by between $60 million and $230 million per year. Information is not available on the total annual sales of supplements containing sources of ephedrine alkaloids other than Ma huang.

Countervailing effects may also take place which may reduce the impact of these negative distributive effects on affected firms. For example, the proposed rule may reduce the number of product liability lawsuits brought against manufacturers of dietary supplements containing ephedrine alkaloids. FDA has insufficient information on the current incidence or cost of these lawsuits to estimate the effect of this reduction, if any, on the negative distributive effects generated by consumption changes. Of course, distributive effects that are negative with respect to a given industry will be positive with respect to some other industry.

Finally, social costs may be associated with these distributive effects. For example, some portion of the value of the capital invested in the production of these supplements may be lost and that loss might not be offset by other effects, such as an augmentation to the value of the capital invested in the production of substitutes. However, FDA has insufficient information to estimate the social costs that might be associated with these distributive effects.

Under these assumptions, the proposed action will generate total compliance costs of between $3 million and $80 million, plus unquantifiable utility losses to consumers of these products. Between $3 million and $70 million of these costs will occur in the

first 6 months after publication of the final rule. In addition, the proposed action will produce distributive effects of between $60 million and $230 million per year and social costs might be associated with those distributive effects. Because the sales of these products are increasing rapidly, FDA believes that this is a conservative estimate of cost and distributive effects. Again, extrapolations have not been made on the growth trend because extrapolating short-term trends into the future can result in large errors. Costs and sales reductions of this magnitude may threaten the viability of many firms in this industry. If some of these firms go out of business, temporary unemployment of labor and permanent loss of capital resources may result. FDA has insufficient information to estimate these costs.

4. Option 4—Take Proposed Action, but With a Higher Potency Limit

Another option is to take all proposed actions but adopt potency limits higher than the proposed potency limits. For example, some trade associations representing the dietary supplement industry have previously expressed support for potency limits of 12 mg/serving and 50 mg/day TEA (Ref. 220). With respect to benefits arising from consumption effects (i.e., the likelihood of reducing the number or seriousness of adverse events), FDA has some information to estimate the effect of variations between the proposed potency limits and higher potency limits on the consumption effects associated with those limits. That is, of the 13 reports of adverse events for which exposure data for intakes less than 20 mg per serving were also available, 5 were in the range between 8 and 12 mg per serving intake.

If consumption is sensitive to small changes in the potency limits, then higher potency limits would reduce the benefits resulting from consumption effects because higher potency limits would presumably have a smaller effect on the effects of these products than the proposed potency limits. Therefore, the effect of raising the potency limits on benefits arising from shifts in consumption will be to reduce those benefits below those generated under Option 3.

Raising the proposed potency limits will not affect the one-time compliance costs but might reduce utility losses to consumers of these products and the distributive effects produced by consumption shifts. Again, these changes may occur because higher potency limits might have a somewhat smaller impact on the perceived benefits of these products than the proposed potency limits. However, as indicated above, FDA has insufficient information to estimate the effect of small changes in the potency limits on the consumption effects produced by those limits and cannot estimate the utility losses associated with various potency limits.

5. Option 5—Ban Dietary Supplements That Contain Ephedrine Alkaloids

Based on the framework used earlier, banning dietary supplements that contain ephedrine alkaloids would lead to a somewhat higher lower bound on estimated benefits. In particular, banning these products would reduce the health risks from these products such that the expected number of adverse events are reduced by between approximately 120 cases and 1,400 cases per year.

Banning dietary supplements that contain ephedrine alkaloids will not change the one time compliance costs estimated under Option 3 because all affected products were subject to reformulation and relabeling costs under Option 3. However, banning these products would decrease access to these products by consumers who may perceive benefits, thus substantially increasing the potential utility losses to consumers. With respect to distributive effects generated by consumption changes, the total reduction in the consumption of dietary supplements that now contain ephedrine would probably be approximately 33 percent under this option, that is, at the high end of the range of 10 to 33 percent estimated under Option 3. Therefore, sales of these products would be reduced by between $200 million and $230 million per year. Costs and sales reductions of this magnitude may threaten the viability of many of the firms producing these products. However, countervailing distributive effects are also possible in that some firms that currently produce dietary supplements containing ephedrine alkaloids may also produce or be able to produce substitute products. In that case, those firms would avoid some or all of the costs associated with producing dietary supplements containing ephedrine alkaloids.

6. Option 6—Take Proposed Action, but Do Not Require Warning Statement

The purpose of the proposed warning statement is to focus existing warnings more precisely on the health risks posed by these products, particularly in cases where any use of these products may be contraindicated, and to add warnings to those products which do not already have warning statements. Even with the proposed potency limits and ingredient restrictions, some consumers may be at high risk of suffering an adverse event from consuming these products because of high individual sensitivity to these products, because of an increase in risk associated with simultaneous consumption of drug products, or because of an underlying health condition. Thus, the proposed warning statement is expected to have some benefit independent of the other proposed requirements. Eliminating the proposed mandatory warning statement will affect estimated labeling costs because, under this option, only those labels affected by the claims restrictions would have to be changed. However, the vast majority of the affected products have labels that would be affected by the claims restrictions. Among the products in the market surveys, 94 percent of the products investigated had one or more claims that would be restricted under this option. Thus, labeling costs under this option will be only approximately 6 percent lower than the labeling costs estimated for Option 3.

Finally, under the framework developed earlier, this option will have little effect on the other costs and distributive effects estimated for the proposed action under Option 3 because of the influence of the other factors involved.

7. Option 7—Require Warning Statements Only

Estimating the benefit of eliminating all proposed actions except the required warning statement involves a controversial value judgment concerning the evaluation of risks that are voluntarily accepted in the presence of the amount of information on those risks provided on the proposed warning statement.

Under the assumption that any adverse events that may occur due to such behavior cannot represent net social costs, warning statements will eliminate all net social costs associated with these adverse events. This assumption is based on the notion that the proposed warning statement provides adequate information on the risks of consuming these products and the notion that if those consuming these products have adequate information on the risks involved, then their consumption decisions reflect their personal judgments concerning the relative value of the benefits and risks of consuming these products.

If no existing warning statements provide adequate information while the proposed warning statement will

provide adequate information, then the social benefits of this option would be at least as great as the value of banning dietary supplements containing ephedrine alkaloids. On the other hand, if some existing warning statements already provide adequate information, then the benefits of this option would still be at least as great as the value of banning dietary supplements containing ephedrine alkaloids; however, the benefits of both options would be lower.

Under the assumption that any adverse events that may occur due to such behavior represent social costs, eliminating all actions other than the proposed warning statement will substantially reduce the benefits from those estimated for Option 3. This assumption is based either on the notion that the level of information provided on the proposed warning statement is inadequate to ensure that consumers can make informed consumption decisions, or on the notion that public health risks require intervention even if those risks are voluntarily undertaken in the presence of adequate information on the benefits and risks of the relevant activity. Under this assumption, this option will reduce the health risks from these products such that the expected number of adverse events will be reduced by between 0 cases and approximately 210 cases per year.

With respect to compliance costs, eliminating all actions except the warning statement would eliminate the costs associated with product reformulation and consumer utility losses.

Finally, this option would substantially reduce the distributive effects of this action. Under this option, the estimated total reduction in the consumption of dietary supplements containing ephedrine alkaloids would be between 0 and 15 percent. Therefore, sales of these products would be reduced by between $0 and $110 million per year. A reduction in sales of this magnitude would threaten the viability of fewer firms than the proposed action, as estimated under Option 3.

V. Regulatory Flexibility Analysis

In the economic impact analysis for the December 1995 proposal, FDA estimated the number of dietary supplement manufacturers to be between 150 and 600, with the majority of those firms being small businesses. Based on additional information, these estimates were revised in the economic impact analysis of the final rule on nutritional labeling. The revised estimate was 500 to 850 firms, with 95 percent of those firms classified as small businesses.

The proportion of dietary supplement manufacturers producing products containing ephedrine alkaloids is unknown. The two market surveys identified 85 manufacturers and distributors of dietary supplements suspected of containing ephedrine alkaloids. Assuming that the proportion of these firms that are small businesses is the same as the proportion of firms in the dietary supplement industry that are small businesses, 95 percent of these firms, or approximately 80 firms, are small businesses.

Total compliance costs incurred by small businesses will be virtually equal to total compliance costs incurred by all businesses estimated earlier because the vast majority of the firms affected by the proposed action are small businesses. Relabeling, reformulation, and testing costs are fixed costs on a per product basis and will disproportionately affect small businesses. Total compliance costs of the proposed action were estimated to be between $3 million and $80 million, with between $3 million and $70 million of these costs occurring in the first 6 months after publication of the final rule. However, FDA has insufficient information to estimate the portion of these costs that will be borne by the owners, stockholders, and employees of these firms and the portion that will be passed on to consumers of these products through price increases. In addition, the proposed action will generate consumption shifts that were previously estimated to produce negative distributive effects of between $60 million and $230 million per year. Countervailing distributive effects are also possible. For example, the proposed rule may reduce the number of product liability lawsuits brought against manufacturers of dietary supplements containing ephedrine alkaloids. Based on reported annual retail sales of between $600 million and $700 million for products containing Ma huang, these costs and distributive effects may be significant.

Most of the regulatory alternatives discussed earlier would reduce the impact of this rule on small businesses. The options of taking no action and taking no action other than generating additional information both reduce the impact on small businesses to zero. Requiring only warning statements would substantially reduce compliance costs to between $3 million and $60 million, with between $3 million and $50 million of these costs occurring in the first 6 months, and also substantially reduce negative distributive effects generated by consumption shifts to between $0 and $110 million per year. Taking the proposed action without requiring the warning statement would slightly reduce compliance costs to between $3 million and $80 million, with between $3 million and $70 million of these costs occurring in the first 6 months, but would not affect distributive effects because of the other factors influencing those effects. Taking the proposed action but raising the proposed potency limit to the level suggested by a trade group representing the dietary supplement industry would probably not significantly alter the impact of this rule on small businesses. Finally, banning dietary supplements containing ephedrine would not change reformulation or relabeling costs and would lead to distributive effects from consumption shifts in the range of $200 million to $230 million per year. This action would have the greatest negative impact on small businesses.

VI. Conclusions

The estimated benefits of Option 3, take the proposed action, are between $240 million and $670 million *per year.* The estimated quantifiable costs are between approximately $3 and $70 million in the first year, and between a minimal amount and about $0.5 million in every year after the first year. Thus, notwithstanding the considerable uncertainty concerning the marginal effectiveness of the individual requirements of the proposed rule, FDA is confident that it would generate benefits that far exceed the quantifiable costs. In addition to the quantifiable costs, however, the proposed action will also generate non-quantifiable utility losses for some consumers and distributive effects from consumption shifts with an estimated value of between approximately $60 million and $230 million per year, with possible countervailing distributive effects from a reduction of liability lawsuits. Social costs might be associated with these distributive effects.

VII. Environmental Impact

The agency has carefully considered the potential environmental effects of this action. Based on the available information, FDA has concluded that the action will not have a significant impact on the human environment, and that an environmental impact statement is not required. The agency's finding of no significant impact and the evidence supporting that finding, contained in an environmental assessment, may be seen in the Dockets Management Branch (address above) between 9 a.m. and 4 p.m., Monday through Friday (Ref. 221).

The agency will reevaluate its environmental decision if new information is received suggesting that the action would have significant environmental effects.

VIII. Paperwork Reduction Act

This proposed rule contains no information collection or recordkeeping requirements under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501 *et seq.*).

IX. References

The following references have been placed on display at the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

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List of Subjects in 21 CFR Part 111

Drugs, Packaging and containers, Incorporation by reference, Labeling.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR part 111 be revised as follows:

PART 111—RESTRICTIONS FOR SUBSTANCES USED IN DIETARY SUPPLEMENTS

Subpart A—General Provisions—[Reserved]

Subpart B—Current Good Manufacturing Practice for Dietary Supplements

Sec.

111.50 Packaging for iron-containing dietary supplements.

Subpart C—New Dietary Ingredients—[Reserved]

Subpart D—Restricted Dietary Ingredients

111.100 Dietary supplements that contain ephedrine alkaloids.

Authority: Secs. 201, 402, 403, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 342, 343, 371).

PART 111—RESTRICTIONS FOR SUBSTANCES USED IN DIETARY SUPPLEMENTS

Subpart A—General Provisions—[Reserved]

Subpart B—Current Good Manufacturing Practice for Dietary Supplements

§ 111.50 Packaging of iron-containing dietary supplements.

(a) The use of iron and iron salts as iron sources in dietary supplements offered in solid oral dosage form (e.g., tablets or capsules), and containing 30 milligrams or more of iron per dosage unit, is safe and in accordance with current good manufacturing practice only when such supplements are packaged in unit-dose packaging. ''Unit-dose packaging'' means a method of packaging a product into a nonreusable container designed to hold a single dosage unit intended for administration directly from that container, irrespective of whether the recommended dose is one or more than one of these units. The term ''dosage unit'' means the individual physical unit of the product (e.g., tablets or capsules). Iron-containing dietary supplements that are subject to this regulation are also subject to child-resistant special packaging requirements codified in 16 CFR parts 1700, 1701, and 1702.

(b)(1) Dietary supplements offered in solid oral dosage form (e.g., tablets or capsules), and containing 30 milligrams or more of iron per dosage unit, are exempt from the provisions of paragraph (a) of this section until January 15, 1998, if the sole source of iron in the dietary supplement is carbonyl iron that meets the specifications of § 184.1375 of this chapter.

(2) If the temporary exemption is not extended or made permanent, such dietary supplements shall be in compliance with the provisions of paragraph (a) of this section on or before July 15, 1998.

Subpart C—New Dietary Ingredients—[Reserved]

Subpart D—Restricted Dietary Ingredients

§ 111.100 Dietary supplements that contain ephedrine alkaloids.

The ephedrine alkaloids include ephedrine, pseudoephedrine, norpseudoephedrine, norephedrine, methylephedrine, methylpseudoephedrine, and related alkaloids. These substances are chemical stimulants contained in

particular botanical products, including those from the botanical species *Ephedra sinica* Stapf., *Ephedra equistestina* Bunge, *Ephedra intermedia* var., *tibetica* Stapf., *Ephedra distachya* L., and *Sida cordifolia* or their extracts.

(a)(1) Dietary supplements that contain 8 milligrams (mg) or more of ephedrine alkaloids (the total of ephedrine, pseudoephedrine, norpseudoephedrine, norephedrine, methylephedrine, methylpseudoephedrine, and related alkaloids) per single serving shall be deemed to be adulterated under sections 402(a)(1) and 402(f)(1)(A) of the Federal Food, Drug, and Cosmetic Act.

(2) The Food and Drug Administration will use high performance liquid chromatography (HPLC) to determine the level of ephedrine alkaloids in a dietary supplement as specified in its Laboratory Information Bulletin (LIB) No. 4053, which is incorporated by reference in accordance with 5 U.S.C. 552(a) and 1 CFR part 51. Copies may be obtained from the Director, Office of Constituent Operations, Industry Activities Staff (HFS–565), Center for Food Safety and Applied Nutrition, Food and Drug Administration, 200 C St. SW., rm. 5827, Washington, DC 20204, or may be examined at the Center for Food Safety and Applied Nutrition's Library, Food and Drug Administration, 200 C St. SW., rm. 3321, Washington, DC, or at the Office of the Federal Register, 800 North Capitol St. NW., suite 700, Washington, DC.

(b) The labeling of dietary supplements that contain ephedrine alkaloids shall not suggest or recommend conditions of use that would result in an intake of 8 mg or more ephedrine alkaloids within a 6-hour period or a total daily intake of 24 mg or more of ephedrine alkaloids.

(c) The label of dietary supplements that contain ephedrine alkaloids shall state ''Do not use this product for more than 7 days.''

(d) No ingredient, or ingredient that contains a substance, that has a known stimulant effect (e.g., sources of caffeine, yohimbine) may be included in a dietary supplement that contains ephedrine alkaloids.

(e) No dietary supplement that contains ephedrine alkaloids may purport to be, or be represented as, either expressly or implicitly, for use for long-term effects, such as weight loss or body building.

(f)(1) The label or labeling for dietary supplements that contain ephedrine alkaloids that purport to be or are represented, either expressly or implicitly, to be used for short-term effects, such as increased energy, increased mental concentration or enhanced well-being, shall state ''Taking more than the recommended serving may cause heart attack, stroke, seizure, or death.''

(2) This information shall appear on the same label panel or same page of labeling as the claim and shall be connected to the claim by use of an asterisk. This information shall appear in easily legible print or type, in distinct contrast to other printed or graphic matter, and in a type size no less than is required by § 101.105(i) of this chapter for the net quantity of contents statement, except where the size of the claim is less than two times the required size of the net quantity of contents statement, in which case the information shall be no less than one-half the size of the claim, but no smaller than one-sixteenth of an inch. Where the label or labeling contains multiple claims, the information shall appear once on each label panel or on each page of labeling.

(g)(1) The labeling of any dietary supplement that contains ephedrine alkaloids shall bear the following warning:

WARNING: If you are pregnant or nursing, or if you have heart disease, thyroid disease, diabetes, high blood pressure, depression or other psychiatric condition, glaucoma, difficulty in urinating, prostate enlargement, or seizure disorder consult a health care provider before using this product. Do not use if you are using monoamine oxidase inhibitors (MAOI) or for 2 weeks after stopping a MAOI drug; certain drugs for depression, psychiatric or emotional conditions; drugs for Parkinson's disease; methyldopa; or any product containing ephedrine, pseudoephedrine or phenylpropanolamine (ingredients found in allergy, asthma, cough/cold and weight control products). Stop use and call a health care professional immediately if dizziness, severe headache, rapid and/or irregular heart beat, chest pain, shortness of breath, nausea, noticeable changes in behavior, or loss of consciousness occur. Do not exceed recommended serving.

(2) The phrase ''Do not exceed recommended serving'' is not required to appear in the warning statement when the disclaimer required in paragraph (f)(1) of this section appears on the same label panel as the warning statement.

(3) The warning statement required by paragraph (g)(1) of this section shall appear prominently and conspicuously on the product label and shall be set off in a box by use of hairlines.

Dated: April 22, 1997.

Michael A. Friedman,

Deputy Commissioner for Operations.

Donna E. Shalala,

Secretary of Health and Human Services.

Note: The following Appendix will not appear in the annual Code of Federal Regulations.

Appendix—AER's Associated With Ephedrine Alkaloid-Containing Dietary Supplements

ARMS No.	Product manufacturer	Clinical summary
9101	Thermojetics Herbal Tablets-Green—Herbalife International.	33 yo F used product (bid, ?dose) in 11/93 until 1st week in 1/94, when she started having dizzy spells that progressed to involve numbness of L arm & forehead, weakness of both legs, SOB, and shaky feelings. 1/30/94 seen in ER for dizziness & tachycardia, Dx labyrinthitis, Tx Valium, d/c on Antivert. 2/2/94 episodes worsened, including dizziness, severe tachycardia, and SOB. She was transported to hospital & admitted w/extensive w/u (CAT, XR echo, doppler, halter, labs). D/c on 2/8 on Tenormin and Ativan w/Dx of SVT. Normal PE in 10/93. No h/o allergies or CV disease. Mother (insomnia) & husband (blood in stool) using product w/various SSx. Sister took product w/o problems.
9316	E'OLA AMP II Pro Drops—E'OLA Biogenics, Inc.	23 yo F hospitalized w/ cardiac arrest, CPR, then ICU. Dx inferolat MI. CK > 2000 (MB+), EKG: sinus tachy & ↑ST inf leads; angio: lacerated coronary (partial dissection) & hematoma at bifurcation of circumflex artery. Used AMP II 3-4 drops in beverage night before arrest, also noted to be using other 'diet pills' (?dose/durations). Drug screen negative, doing well off product.

ARMS No.	Product manufacturer	Clinical summary
9552	Nature's Nutrition Formula One—Affiliated Consultants Inter./Alliance U.S.A. Inc.	35 yo F good health, no risk factors for CAD used product 04/94—05/94 (30 days) for WL&E, as much as 1–2 caps bid 30 days. She stopped for a week but resumed again at 3 caps qd. On 6/25/94, developed acute onset of throbbing, ant. CP at rest, w/ pain radiation to the left shoulder, numbness of left arm & hand, diaphoresis and SOB. The pain persisted, and she was taken to the ER. The pain decreased with subl nitro and was completely relieved with morphine and nitro. On admission, BP: 140/100, EKG: minor ST depressions V_1, V_2, and minor ST elevation in INF leads, elevated cardiac enzymes. Dx: Acute non-Q wave MI probably secondary to coronary spasm. Cardiac cath 6/27/94 LV angiogram very mild posterior basilar hypokinesis, normal LV function w/ good ejection fraction. Normal coronary arteries. Discharged after 4 days on Cardizem, aspirin, nitro prn, & f/u for a limited stress test.
9747	Ripped Fuel—Twin Laboratories, Inc	40 yo F reported by physician to suffer a grand mal seizure after using product for 3 days (2 bid) as directed. Her husband stated she stopped breathing and he had to administer mouth to mouth resuscitation. She was on no medication and had no personal nor family history of seizures. She had no symptoms until she felt dizzy immediately before her seizure. CT head—no abnormalities.
9751	Slim NRG—Momentum Marketing	28 yo F (weighing 95 lb) reported by MD. Used product, 1 tid for 6 months for weight loss (30 lb). Stopped product abruptly, became despondent over 10 days ending w/ attempted suicide—gunshot wound to chest. No other products used. Past mental history negative for mental illness, use of drugs/alcohol. Drug/ETOH screen neg. Tx: w/antidepressants. Positive dechallenge.
9754	Shape-Fast—Shaperite Concepts Ltd	44 yo F reported by physician's assistant to be taking product (400 mg bid) when she developed heat stroke, chest and back pain, hyperthermia and tachycardia while exercising.
9818	Power Trim—Enrich International	43 yo M who used product (details not given) over a 6 wk period and lost 30 lb., developed new onset insomnia and atrial fibrillation. Seen by health care provider and given Lanoxin, hospitalized next day when light headedness developed. Extensive w/u (EKG, CXR, echo-cardiogram, smac, myocardial enzymes), compatible with AF. Dx: ''new onset atrial fibrillation, possibly due to the stimulant effect of his dietary supplement.'' Tx: Lanoxin, Betapace, Verapamil, and Coumadin.
9864	Nature's Nutrition—Formula One—Affiliated Consultants Intl/Alliance U.S.A.	44 yo M, active swimmer and tennis player, with no known cardiovascular risks as documented by medical history, originally obtained a sample of product during a routine physical from his health care provider when he requested some substitute for his daily coffee and cocoa use. He used this product as directed, and was able to eliminate his afternoon coffee/cocoa use. On 12/18/93 (~3 weeks after starting product), after playing his routine weekly game of tennis, he came home, laid down and was found dead about noon. Resuscitative efforts were unsuccessful. Autopsy revealed an acute thrombus, 1.5 cm from the origin of the left anterior descending coronary artery, resulting in occlusion. All lumina were otherwise patent, although calcification of the coronary arteries resulting in focal narrowing to about 50 percent was noted. A drug screen performed at the time of autopsy was reportedly negative for amines.
10009	MetaboLift Thermogenic—Twin Laboratories, Inc.	35 yo M w/acute MI (inferoapical). Took product (two capsules at noon and 3 capsules at 4:30 PM) Worked out 5:30 PM—6:30 PM and developed chest pain around 7:30 PM. Consumer admitted, treated w/TPA, subsequent cardiac catheterization demonstrated normal coronaries. CPK elevated, EKG diagnostic for MI.
10026	Formula One—Affiliated Consultants Intl./Alliance U.S.A.	48 yo F took product (3 caps qd) for 6–7 months when developed weakness, syncopal episode, increased BP, increased HR, tightness in chest. Seen in ER w/ EKG which showed nonspecific STT wave abnormality, and increased cardiac enzymes. BP–120/99. Saw MD next day, complained of right sided weakness and speech difficulty. Meds: antihypertensives, hormones. Dx: ''conversion reaction'', thought to be stress related. Sxs improved over next month. MD later told about use of product, which he states could aggravate nervousness.
10063	Super Diet Max—KAL, Inc	22 yo F had been using product several months at 1 tab bid for WL. On day of adverse event she had taken 2 caps (1 q AM, 1 q PM), and experienced increased BP, pounding heart, n/v, lasting 1.5–2 hr. Event abated after product discontinued. Saw health care provider. Started on Prozac 2 wks prior to adverse event.
10088	Nature's Sunshine SN–X 100 Vegitabs—Nature's Sunshine.	38 yo F took product for 4 days and developed syncope, blood pressure = 180/110. Seen in ER with severe HA, nausea, diaphoresis. The consumer had been seen every 3–4 months for 5 years prior to this event and no history of high blood pressure. After stopping the product her blood pressure returned to normal.
10275	Nature's Nutrition Formula One—Affiliated Consultants International/Alliance U.S.A.	63 yo F reports using product for 3 weeks at recommended dose, never used maximum recommended dose, when she developed hives. The next day she had difficulty walking across room, difficulty breathing and swallowing, and vomited. She suffered ventricular fibrillation, a small non Q-wave infarct by enzymes criteria and was hospitalized 5 days where evaluation (cardiac catheterization, electrophysiology study) failed to find any sort of heart problem or heart disease to explain her arrest. She has chronic obstructive pulmonary disease secondary to cigarette smoking. Previous to arrest no medicine and only vitamin and occasional aspirin.

ARMS No.	Product manufacturer	Clinical summary
10437	Thermojetics Herbal Tablets—Beige, Thermojetics Herbal Tablets—Green, Formula 1, Formula 2, Formula 3—Herbalife International.	55 yo F reports grand mal seizure after 3 days on product per directions. No significant past history, normal CT and EEG. No meds or other dietary supplement products.
10862	Ultimate Xphoria—Alternative Health Research.	20 yo M took 8 tabs @ ~4 pm (directions: Take 4 tablets, on an empty stomach; do not exceed 4 tablets in 24 hours). Within ~30 minutes, complained of being hot, w/ sweating & HA. Found dead by friends ~8 hr later. Coroner's report notes toxic levels of ephedrines.
10919	Power Trim—Enriched International	49 yo F used Power Trim, 3 capsules three times daily for 3 weeks for weight loss. She developed weakness, dizziness, nausea, vomiting, and palpitations and went to the ER where she was found to have vertigo, serous otitis media bilaterally, hypertension (150/102) and elevated liver enzymes. The consumer reports stopping the product and her blood pressure has returned to normal without any medical treatment. She has no history of high blood pressure.
10943	Multi DS—(1) Omnitrim Tea & (2) Omni 4—Omnitrition International, Inc.	37 yo F used for 1 week, Omnitrim Tea, 2 teaspoons three times per day, and Omni 4 (a vitamin) one daily, both as directed, for weight loss. She stopped due to the development of shakes, sweats, dizziness, racing heart, and loss of hearing in R ear. Symptoms abated after stopping product. No other products in use and no significant medical history.
10946	Multi DS—(1) ThermoChrome 5000, (2) Isotonic Vitamin B12, & (3) Isotonic OPC3 (1) Health Power Products Inc./ Market America; (2) & (3)—Labels unavailable.	42 yo F used Thermochrome 5000, 1 capsule twice daily for 3 days for weight loss. She was also taking B12 and an antioxidant supplement. She developed a rash over her entire body and stopped all three products. She restarted the Thermochrome 5000 after 3 days and 3 days after that, on a visit to her doctor for a nonproductive cough and congestion, was found to be hypertensive (170/114). She has no history of hypertension and was seen by her gynecologist 1 week before starting the Thermochrome with a normal blood pressure (120/78).
10957	E'Ola Amp II Pro Drops—E'OLA Biogenics, Inc.	34 yo F used E'Ola AMP II Pro Drops according to label directions, off and on over a 2 year period for weight loss. She developed ''triple vision'' which lasted a few moments and recurred 3 days later accompanied by vertigo. She was initially seen in an ER, where examination and CT were normal and she was diagnosed with dehydration. She spent 3 days in bed with severe vertigo, nausea, and vomiting. She was unable to reach out and pick up a drinking glass. An MRI showed multiple bilateral cerebellar infarcts. No source of embolization was identified. Cardiovascular, autoimmune, and coagulopathy workups were unremarkable.
10960	Blast and Burn—Vita Labs Inc	16 yo F used Blast and Burn as directed on the package for several weeks for performance as a high school athlete. Within the first week of use she was taken to the ER with a racing heart. She had several similar episodes. She couldn't afford to buy a second bottle of the product and noticed her symptoms resolved once she stopped using the product.
10974	ShapeFast—Shaperite Concepts Ltd	19 yo F took Shaperite, one before each meal, three times per day (½ of recommended amount) for 1 month, for weight loss. Her family witnessed seizure activity at mealtime and took her to the ER. CT and EEG were normal. Neurologist's evaluation found no other risk factors for seizure. No other products used, no significant past history noted.
10977	Emphora Ecstasy—Label unavailable	18 yo F took Emphora Ecstasy, 4 pills at once, to get high. About 2 hours later she noted dizziness, racing heart and felt she would pass out if she stood up. She was unable to sleep for most of that night. The next morning she passed out in the shower, injuring her neck and back. She went to the ER where the only abnormality noted was a low potassium of 3.1 meq/L (normal 3.6–5.2). She has had dizziness in the past but no previous loss of consciousness. The product was not used again and her symptoms resolved.
10989	Herbal Ecstasy—Label unavailable	18 yo F used Herbal Ecstasy, 5 pills at once, one time as directed to get high at a Lolapalooza concert. She felt ''numb, weird'' and fell backwards. She was unable to sleep for 3 nights in a row. Over the next 8 months, she had difficulty sleeping, refused to leave the house unless her parents insisted and did not attend college as planned in the fall. She has been diagnosed with panic attacks and depression and is currently under psychiatric treatment. She has also been diagnosed with a ''weak heart valve.''
10990	Tri-Chromaleane—Achievers Unlimited	58 yo M used Tri-Chromaleane, 3 pills once daily for 6 weeks for weight loss. He developed memory problems. He couldn't remember his son's middle name, his office phone number or how to get home from a local store. He would start work and be unable to remember why he had started the task or what to do next. He stopped the product and his symptoms resolved over the next 2 weeks. At the same time he had been participating in a clinical trial of Proscar for the prevention of prostate cancer and does not know whether he had been taking Proscar or placebo. The Proscar study coordinator reported that it was unlikely that the consumer's complaints were related to Proscar. Of note, he never had prostate cancer.

ARMS No.	Product manufacturer	Clinical summary
10991	Tri-Chromaleane—Achievers Unlimited	54 yo F used Tri-Chromaleane, at less than the recommended amount, once daily for a number of weeks. She was under treatment for hypertension and was told by the distributor that the product would *lower* her blood pressure. After starting the product her blood pressure increased and her doctor added a second medication and her blood pressure improved. She was unable to pass an insurance physical due to her inadequately controlled high blood pressure. She stopped the Tri-Chromaleane and her blood pressure has improved to the point that her doctor is planning to stop the second blood pressure medication to see if she can be controlled on a single medication (as she was before using the Tri-Chromaleane).
11050	ThermoChrome 5000—Health Power Products.	63 yo F took 2–3 pills bid, for 2 months for weight loss. She was taking Lescol for hypercholesterolemia, Zantac for esophageal reflux and Vasotec for hypertension. She developed worsening of her hypertension (174/93) and episodes of palpitations. She sought medical assistance from a neighbor who is a physician after an especially severe episode of palpitations. After stopping products BP normalized (140/80) and palpitations resolved.
11062	Power Trim—Enrich International	42 yo F used 2–3 caps before meals tid as directed for 3 months for weight loss. She was taken to hospital by ambulance after family members found her seizing. She had another seizure while being examined by neurologist. She complained of increased headaches and slow thinking in the days preceding her stroke and was taking penicillin for a dental abscess. CT and MRI showed a small R-sided intracerebral hemorrhage. MRI and angiography revealed no evidence of any vascular abnormality. She was treated with Dilantin.
11065	Thermo Slim—Weight Loss Specialist	23 yo F used product, 1 tab before meals 3 times per day with The Accelerator Guarana, 1 tab before AM and noon meals, for 8 days. On the 9th day she forgot to take her noontime dose. At first she thought she might be going into withdrawal, took another dose and vomited shortly afterwards. She was taken to the ER with complaints of a racing heart, dizziness, numbness of face and arms, and disorientation. The doctor advised her to stop the products and over the next week her symptoms resolved.
11078	Formula One with Quick Start—Alliance U.S.A.	36 yo F used Formula One for 2 yrs, stopped that product and then took Quick Start 2 caps which she used once. The next morning she experienced grand mal seizures. She was taking 2 iron tablets, Ionamin 30 (a dietary supplement) and B12 liquid; also had switched to the night shift. CT, MRI, and EEG were normal.
11081	Herbal Ecstacy—Label unavailable	M used Herbal Ecstacy, 10 pills once, to get high. He states he became ''psycho,'' very active, developed a ''bad mood'' and assaulted a friend. His symptoms resolved and he did not try the product again.
11105	Trim Easy—TeamUp International Inc	31 yo F used Trim Easy for about 1 year for weight loss. She originally used 2 capsules three times daily for 1 month and then increased to 3 capsules three times daily (9 total). The directions advised beginning at 2 capsules three times per day and increasing if tolerated to 3 capsules three times per day, the maximum recommended dose. At times she would forget one of the 3 doses and double up the next time she took the product (6 capsules at once). She continued to take a total of 9 capsules this way daily for about 3 months and then decreased to a total of 6 capsules taken all at once each day for about 8 months. She developed dizzy spells which increased over 1 month's time to twice daily and eventually suffered a stroke—an intracerebral hemorrhage with Lft hemiparesis and aphasia. CT and MRI documented the bleed, showing midline shift. Cerebral angiogram did not show any additional abnormality such as an arteriovenous malformation.
11106	Therma Slim—Great American Products ...	47 yo F used 1 pill at breakfast and 1 at lunch for 2 months. She developed profuse sweating, trembling and HTN, and menstrual bleeding which lasted 6 wks. She was treated first with Megesterol and then with Premarin and Provera, by gynecologist. It was also noted that her BP had risen from 110/70 (3/18/96) to 156/98 (4/10/96). She complained to radio station where she originally heard about product and received a letter telling her side effects she was experiencing were normal and would quickly subside. 4/11/96—Consumer contacted her HMO after seeing broadcast on ephedra and was advised to stop using product. 6/1/96—This consumer later suffered a pontine stroke and requires an endotracheal tube and feeding tube for long-term ventilatory and nutritional support, respectively. Estrogen use was implicated as a possible contributing factor by health care provider.
11107	Diet Fuel—Twin Laboratories, Inc	42 yo M used Diet Fuel, 3 pills daily for 9 months. He became dizzy, nauseated, developed left sided chest pain, passed out in a meeting. Paramedics noted his pulse to be in the 30's and he was hospitalized. After cardiology evaluation and electrophysiologic studies it was concluded that the consumer had an abnormal vasodepressor response to tilt plus catecholamine administration and was placed on Tenormin. The consumer reports a similar episode many years prior and as a young man treated with Dilantin for what was diagnosed as epilepsy.
11109	Unspecified E'OLA product—E'OLA Biogenics, Inc.	46 yo F used two E'OLA products, an energy product, 2 drops twice daily, and a metabolism booster, 4–5 drops twice daily, both for 1½ weeks, for energy and weight loss. She developed a heart rate of 200 beats per minute and sought medical attention. Medical records describe evaluation for recurrent paroxysmal palpitations for 20 years. No mention of the use of E'Ola products. Blood pressure, pulse, EKG, echocardiogram, exercise stress test failed to reveal an underlying cardiac disorder.

ARMS No.	Product manufacturer	Clinical summary
11112	Thinner Jizer—Quiet Storm	34 yo F used Thinner Jizer 1 pill for 1 day, 1 pill twice daily, then 2 pills in AM and 1 pill in PM, increasing as directed. After 3 days on the highest amount (2 pills AM and 1 pill PM) she developed jitters and was advised by the distributor to cut back the dose as this response was normal. She used 1 pill AM and 1 pill PM for an additional 3 days when she developed acute visual changes in her right eye lasting 25 minutes. She sought medical care and was advised that her symptoms were likely due to vascular spasm, possibly related to her use of ephedra. She stopped the product, took aspirin for 1 week and has had no further episodes of acute visual changes. She was taking no other products and has no significant prior history.
11114	Herbal Ecstacy—Label unavailable	16 yo M used Herbal Ecstacy, 2 pills one time. Half an hour later he found himself driving down the wrong side of a road and didn't realize it until he saw a car headed towards him. He described feeling ''a major rush, tingly, hyper.'' He denies taking other products including drugs, alcohol, or street-type drugs at the time. He occasionally uses ginkgo biloba, but had not taken any that day.
11131	Multi DS—(1) Herbal Ecstacy & (2) Nirvana—(1) Global World Media & (2) Label unavailable.	20 yo M used Herbal Ecstacy, 5 pills one time as directed, for recreational purposes. He also took 6 Nirvana pills one time (directions recommend 7 pills) also for recreational purposes. He went to a club and began to feel dizzy, lightheaded and nauseous. He noted stomach cramps, thirst, and a ''real bad headache.'' His symptoms forced him to leave the dance floor, feeling he was going to pass out. He fell on his knees, started ''seeing things'' and felt his seeing and hearing were distorted. He noted shortness of breath, sleeplessness, and hives. His symptoms resolved by the next day. He denies alcohol, other drug or product use that night.
11134	Multi DS—(1) Ripped Fuel, (2) The Ultimate Whey Designer Protein, (3) Super Amino 2000, (4) Super Once-A-Day Timed Release Multiple Vitamins and Chelated Minerals—(1) Twin Laboratories, Inc. (2) Next Nutrition Inc. (3) Ultimate Nutrition Products Inc. (4) Quest Vitamins LTD.	23 yo M college student who used multiple dietary supplements for approximately 2 years with observed daily use during the year prior to being found dead at home by his sister. There was no previous medical history and no evidence of trauma or substance abuse. Toxicology screens were negative for alcohol, barbiturates, cocaine, methamphetamine, morphine, and salicylate but indicated the presence of ephedrine alkaloids in the urine. The Medical Examiner's reports states the cause of death as, ''patchy necrosis associated with ephedrine toxicity from protein drink containing ma huang extract.'' Review of health examination reports from the University Health Service indicate the consumer was in excellent health with normal weight, height, blood pressure, and laboratory measurements.
11137	Natural Trim—Starlight International	39 yo F used product for 6.5 months, 1 thermogenic pill, 1 vitamin and 1 booster pill at 10 AM, and 1 thermogenic pill at 4 PM, as directed. While on antibiotics for a sore throat, she developed upset stomach and stopped the products. She became shaky, weak, and exhausted, and felt as if she were about to pass out if she tilted her head. She was diagnosed with hyperthyroidism. She also reports her supplier has stopped selling the product as the seller has suffered seizures.
11140	Power Trim—Enrich International	59 yo F used Power Trim and later Power Prime and has had a total of 3 vertigo attacks: 2/96, 4/96, and the third at an unspecified time. She has been to the ER and seen her physician.
11144	Metabolift—Twin Laboratories, Inc.	28 yo M used Metabolift for 10 months, 1 cap 1–2 times daily for energy. While visiting a rental property with his father's truck, his father had found him bloody, walking away from the garage, and responding inappropriately. He has transient retrograde amnesia. In the emergency room his blood pressure was 168/90, and pulse was 116. CT head EKG were normal. He was diagnosed with syncope and a closed head injury. The next week the consumer had an EEG, echocardiogram, and MRI of the head—all normal. His neurologist stated ''most likely he had a seizure secondary to the ephedrine'' from the health food substance he was taking. He was advised to avoid the product and dispose of it. He was on no other medication, has no significant past medical history and has never had problems with dizziness or passing out.
11180	Nature's Nutrition Formula One—Alliance U.S.A. Inc.	41 yo F used Nature's Nutrition Formula One (Alliance) 1–2 pills in AM and 1–2 pills PM for about 6 months for energy. One morning she took 2 pills, skipped breakfast and drank a diet Pepsi. Soon after she developed hives while visiting a nursing home and was given benadryl tablets. Two hours after taking the Formula One she was found unconscious in a stairwell by nursing personnel who described seizure activity. She was taken to an ER where the evaluation including EEG and CT scan was normal. She has not used the product again and has had no further episodes.
11181	Multi DS—(1) Ripped Fuel & (2) Unspecified chromium picolinate with caffeine product—(1) Twin Laboratories, Inc., (2) GNC.	19 yo M used Ripped Fuel 2 pills 2–3 times daily, according to label directions, for 2 days for weight-loss and body-building. He was found by family members on the morning of the third day, in his bed with seizure activity and afterward complained of dizziness and a headache. He was taken to the ER and given IV Dilantin. CT and MRI were normal and EEG was nonparoxysmal. He had also been taking chromium picolinate, 1 pill daily as directed for 3–4 months; Phosphagen, 1 teaspoon with meals, three times per day as directed for 3–4 months; and B2G vanadyl sulfate, 2 capsules with meals, three times per day, as directed for 1 month at the time of the event. Based upon the test results and history of use of the Ripped Fuel, his neurologist felt the patient did not need to be treated with Dilantin. The neurologist advised the patient to stop use of all ''over-the-counter medications''. The patient suffered a second witnessed seizure 1 month later and was started on Dilantin. His past history is significant for a concussion as a child with a normal CT at the time.

ARMS No.	Product manufacturer	Clinical summary
11215	Multi DS—Ripped Fuel and Ripped Force—Label unavailable.	24 yo M used Ripped Fuel, 2 tablets three times daily for 2 years and Ripped Force, 1 bottle daily for 2 months. He used both products for body building. He went on vacation, stopped the products and within 3 days experienced 2 grand mal seizures. The second seizure was witnessed by the ambulance crew while en route to the ER. MRI of head and EEG were both reportedly normal. He was also using 'vanadyl', creatine, and amino acids as part of his body building regimen. He denied use of recreational drugs, medications, or other products.
11248	(1) Formula One, (2) Equilizer, (3) Protein Plus Chromium Picolinate, (4) Fast Start—(1) Alliance U.S.A., Inc, (2), (3), (4) Equinox Intl.	37 yo M used products 2 yr (and had used other products containing ephedrine prior to use of Formula One). (Formula One use: 1–2 cap mid AM & PM, per label instructions). Also known to consume large amount of diet cola. Experienced apparent sudden cardiac arrest, with no details known surrounding death. Coroner's report notes: cardiomegaly w/mild LVH, focal interstitial fibrosis & mild medial hypertrophy. PMH: neg for HTN. Tox screen noted pseudoephedrine in urine.
11249	Victory Turbo Pump—Joe Wider Nutrition	20 yo M took product for 3 months (once or twice per week), experienced grand mal seizure. Neg. past history and family history for seizure disorders. He was treated with Dilantin.
11286	Breathe Easy Herbal Tea—Traditional Medicinals.	36 yo F used Breathe Easy Herbal Tea on one occasion at less than recommended dose. She steeped tea for 1 minute and drank ⅓ cup instead of steeping tea for 5 min as indicated on the instructions. She used product along with 2 Advil to relieve cold/congestion symptoms. Approximately 15 min after drinking tea she experienced rapid, pounding heartbeat. Following advice of friend who is a nurse, she drank large amounts of water in effort to ''flush tea out of her system.'' She felt so bad she could hardly get out of bed, but did not seek medical care secondary to anxiety about hospitals. Symptoms resolved completely within 5 hours. Routine medical visit approx 1 month after event was unremarkable. Past medical history is significant for occasional palpitations. Consumer's husband used product on several occasions prior to event with no report of negative side effects.
11298	(1) Fast Start-The Equilizer, (2) Nigh Time, (3) Protein Plus, Chromemate—Equinox International.	41 yo M used 3 herbal products as directed on labels in an attempt to lose weight. He experienced a ''rush'', and blurred vision which influenced his ability to operate heavy equipment. On 5th day of using the product, his underwear was noted to be stained red. A physician visit confirmed hematuria, and noted BP of 136/102, and labs: SGPT 72, cholesterol 208, triglycerides 401. He stopped the product, with recovery, including normalization of BP.
11401	Ultra Energy Now—Phoenix Health Products.	42 yo M used Energy Now tablets on 2 separate occasions. He took 3 tablets as instructed on label on both occasions. First occasion was without incident. 2 weeks later when he used product for second time, he experienced severe diaphoresis, blurred vision, SOB, lightheadedness, and pounding chest pain within 1 hour of taking product. Symptoms lasted approx 15 min and had resolved completely by the time he was seen in emergency room. He was admitted to hospital overnight for evaluation including EKG, CBC, & SMA–18 which was all within normal limits. Of note, he was not using any other products. History is significant only for positive tobacco history=1.5 pack of cigarettes per day.
11417	Thermojetics Herbal Tablets—Green—Herbalife International.	34 yo F died following diagnosis of primary pulmonary hypertension (PPH). Mother of deceased found bottles of Herbalife Green & Beige tablets in home of the deceased. Duration and detail of use are unknown. Deceased appeared to be in excellent health until approx. 3 months prior to her death when she developed SOB & n/v while skiing in Colorado despite numerous previous ski trips in same location which were uneventful. She was diagnosed with ''high altitude sickness.'' Symptoms persisted and she subsequently underwent cardiac catheterization 3 months after onset of sxs. Results of cath were apparently consistent with PPH and indicated that she would need heart/lung transplant in 3–5 years. She died 3 days later in August 94. Past medical history is significant only for hospital admission 1 year prior to death for CP, SOB, and possible pneumonia.
11441	Ripped Fuel—Twin Laboratories, Inc	27 yo M died secondary to injuries sustained in motor vehicle accident. Wife of deceased reports he had been taking Ripped Fuel 2 tabs bid as instructed on label for approx. 3 years prior to death. No autopsy was performed. Post mortem blood analysis indicate: 0.05 percent ethyl alcohol & 0.31 percent mg/L phentermine. Post mortem urine analysis: Positive for phentermine, negative for cocaine, opiates, benzodiazepine, cannabinoids.
11442	Thermojetics Herbal Tablets—Green—Herbalife International.	39 yo F used Herbalife Diet Plan which consisted of the following 5 products: Formula 1 Protein Drink Mix (2 tablespoon bid); Formula 2 Multivitamin-Mineral Tablet (1 tablet tid); Formula 3 Cell Activator Capsules (2 capsule bid); Herbal Beige Tablet (1 tablet bid); Herbal Green Tablet (3 tablet bid) all taken as directed on label. No other products were being used at the time she developed the adverse events. 3–4 months after starting plan, she began experiencing blurred vision and headache. 2 weeks later she began experiencing dizziness, lightheadedness, slurred speech, and numbness on right side of her body. Evaluation by neurologist indicated patchy sensory deficit in right leg, most pronounced in foot. MRI of brain showed findings consistent with recent hemorrhage associated with cavernous malformation. Evaluation by internist indicated negative w/u for Lyme disease and no additional significant findings. Symptoms improved after consumer discontined use of products.

ARMS No.	Product manufacturer	Clinical summary
11619	AMP II Drops—E'OLA Bio-genics, Inc	35 yo F used Liquithin & AMP II Pro (both 7 drops bid) and Citrin Trim (2 tablet/day) for 1 day and developed migraine headache which she typically experiences every month. She awoke at 3 AM on morning after using products with notable right sided facial weakness, CP, palpitations, right arm weakness and numbness, photophobia, and unsteady gait. She was seen by doctor and admitted to hospital. Symptoms improved during hospitalization which was uneventful. All test results were within normal limits except cerebral arteriogram findings which suggested mycotic aneurysmal change or possible changes secondary to an unusual drug induced vasculitis or collagen vascular disease. Discharge dxs included: right facial and arm weakness, cause uncertain; improving right eye irritation; resolving headache; resolved chest pain & palpitations with neg w/u; and history of right C5–6 cervical radiculopathy, carpal tunnel syndrome. Sxs continued to improve in month following discharge. History is significant for: Classical migraine headache associated with right jaw tingling; cardiac murmur with prior evaluation; allergy to iodine dye (tachycardia); and habit of drinking 1.5 quart of caffeinated soda daily.

Abbreviations Used in Clinical Summaries in the Appendix

abn = abnormal
angio = angiography
ant = anterior
AF = atrial fibrillation
bid = twice a day
BP = blood pressure
CAD = coronary artery disease
Cap/caps = capsule(s)
cath = catheterization
CBC = complete blood count
CK (CPK) = creatine kinase
cm = centimeter
CP = chest pain
CPR = cardiopulmonary resuscitation
CT = computerized tomography
CV = cardiovascular
CXR = chest X-ray
d/c = discontinue or discharge
DTR = deep tendon reflexes
Dx(s) = diagnosis(es)
EEG = electroencephalogram
EKG = echocardiogram
EMG = electromyography
ER = emergency room
ETOH = ethanol
F = female
f/u = followup
fxn = function
GPT = alanine aminotransferase
h/o = history of
HA = headache
HTN = hypertension
ICU = intensive care unit
IEP = immunoelectrophoresis
inf = inferior
L = left or liter
LFT = left
lb = pound
LV = left ventricle
M = male
MB+ = MB positive
MD = medical doctor
meq = milliequivalents
MI = myocardial infarction
min = minutes
MRI = magnetic resonance imaging
neg = negative
nitro = nitroglycerin
n/v = nausea and vomiting
PE = physical examination
PMH = past medical history
q = every
qd = everyday
R = right
SGPT = serum GPT
SOB = shortness of breath
SSx = signs & symptoms
ST/STT = ST–T waves
subl = sublingual
SVT = supraventricular tachycardia
tab(s) = tablet(s)
tach(y) = tachycardia
tid = 3 times a day
tox = toxicological
TPA = tissue plasminogen activator
Tx = treatment
w/ = with
w/o = without
w/u = workup
WL&E = weight loss & energy
wnl = within normal limits
yo = years old
yr = year

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