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# DIETARY SUPPLEMENTS CONTAINING EPHEDRA

## Health Risks and FDA's Oversight

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Highlights of [GAO-03-1042T](#), testimony before the Subcommittee on Oversight and Investigations, Committee on Energy and Commerce, House of Representatives

## Why GAO Did This Study

Dietary supplements containing ephedra have been associated with serious health-related adverse events, including heart attacks, strokes, seizures, and deaths. The Food and Drug Administration (FDA) regulates dietary supplements under the Dietary Supplement Health and Education Act of 1994 (DSHEA). Reports of adverse events have been received by FDA and others, including Metabolife International, the manufacturer of a dietary supplement containing ephedra, Metabolife 356.

Because of concerns surrounding the safety of dietary supplements containing ephedra, GAO was asked to discuss and update some of the findings from its prior work on ephedra, including its examination of Metabolife International's records of health-related calls from consumers of Metabolife 356. Specifically, GAO examined (1) FDA's analysis of the adverse event reports it received for dietary supplements containing ephedra, (2) how the adverse events reported in the health-related call records collected by Metabolife International illustrate the health risks of dietary supplements containing ephedra, and (3) FDA's actions in the oversight of dietary supplements containing ephedra.

[www.gao.gov/cgi-bin/getrpt?GAO-03-1042T](http://www.gao.gov/cgi-bin/getrpt?GAO-03-1042T).

To view the full product, including the scope and methodology, click on the link above. For more information, contact Marcia Crosse, (202) 512-7119.

# DIETARY SUPPLEMENTS CONTAINING EPHEDRA

## Health Risks and FDA's Oversight

### What GAO Found

FDA has used the adverse event reports it has received to conclude that dietary supplements containing ephedra pose a significant public health hazard. Since February 1993, FDA has received 2,277 reports of adverse events associated with dietary supplements containing ephedra, 15 times more reports than it has received for the next most commonly reported herbal dietary supplement.

The types of adverse events that GAO identified in the health-related call records from Metabolife International were consistent with the types of adverse events reported to FDA and with the documented physiological effects of ephedra. Although call records contained limited information for most of the reports, GAO identified 14,684 call records that had reports of at least one adverse event among consumers of Metabolife 356. GAO's count of 92 serious events—heart attacks, strokes, seizures, and deaths—was similar to that of other reviews of the call records, including counts by Metabolife International and its consultants. Many of the serious events were reported among relatively young consumers—more than one-third concerned consumers who reported an age under 30. In addition, for call records containing information on the amount of product consumed or length of product use, GAO found that most of the reported serious adverse events occurred among consumers who followed the usage guidelines on the Metabolife 356 label.

As part of its oversight of dietary supplements, FDA has taken some actions specifically focused on dietary supplements containing ephedra. FDA has issued warnings that focus on improper labeling, issued warnings to consumers, and issued a proposed rule in 1997 that, among other things, would require a health warning on the label of dietary supplements containing ephedra and prohibit a dietary supplement from containing both ephedra and a stimulant. FDA subsequently banned the sale of certain classes of over-the-counter drugs containing ephedrine and related alkaloids—the active ingredient in ephedra—in combination with an analgesic or stimulant. As the 1997 proposed rule has not been finalized, there is no rule prohibiting the marketing of dietary supplements with similar ingredients, and many dietary supplements with ephedra, such as Metabolife 356, also include caffeine or other stimulants. To receive comments on new evidence, FDA recently reopened the comment period for the proposed rule, and FDA reported to GAO that the agency is in the process of reviewing comments it has received and has not reached a decision regarding further action.

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Mr. Chairman and Members of the Subcommittee:

I am pleased to be here today as the Subcommittee considers concerns about the safety of dietary supplements containing ephedra. More than half of U.S. adults are overweight or obese, and more than one-third are trying to lose weight. Many Americans have turned to dietary supplements to help them lose weight. The most widely used weight loss supplement ingredient is ephedra, which is also referred to as *ma huang*.<sup>1</sup> The dietary supplement industry has estimated that as many as 3 billion servings of dietary supplements containing ephedra are consumed each year in the United States. Medical experts have expressed concerns about the safety of dietary supplements containing ephedra. Reports of adverse health events associated with such supplements, including reports of heart attack, stroke, seizure, and death, have been received by the Food and Drug Administration (FDA) and others, including Metabolife International, the manufacturer of a dietary supplement containing ephedra, Metabolife 356.

The Dietary Supplement Health and Education Act of 1994 (DSHEA) created a framework for FDA's regulation of dietary supplements as part of its oversight of food safety.<sup>2</sup> Since dietary supplements are generally marketed without prior FDA review of their safety, FDA relies on voluntary reports of adverse events from consumers, health professionals, manufacturers, and others in its effort to oversee the safety of marketed dietary supplements.

Because of concerns surrounding the safety of dietary supplements containing ephedra, you asked us to discuss some of the findings from our prior work on ephedra. My remarks today will focus on (1) FDA's analysis of adverse event reports it has received about dietary supplements containing ephedra, (2) how the adverse events reported in the call records received by Metabolife International illustrate the health risks of dietary supplements containing ephedra, and (3) FDA's actions in the oversight of dietary supplements containing ephedra.

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<sup>1</sup>The active ingredients in ephedra are ephedrine alkaloids. Ephedrine alkaloids that are not from an herbal or botanical source (or a derivative thereof), such as synthetic ephedrine alkaloids, may not be marketed as dietary supplements.

<sup>2</sup>Pub. L. No. 103-417, 108 Stat. 4325.

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This testimony is based primarily on our earlier reports on dietary supplements, including our March 2003 review of health-related call records received by Metabolife International.<sup>3</sup> For this testimony, we also conducted additional analyses of the data in the Metabolife International call records, obtained updated information from FDA about its oversight efforts and adverse event reports that it has received concerning ephedra, and reviewed FDA analyses of the safety of dietary supplements containing ephedra. We conducted our work from June 2003 through July 2003 in accordance with generally accepted government auditing standards.

In summary, FDA has determined that dietary supplements containing ephedra pose a significant public health hazard based on the 2,277 adverse events reports it has received. The number of adverse event reports FDA has received for dietary supplements containing ephedra is 15 times greater than the number it has received for the next most commonly reported herbal dietary supplement. While it is difficult to establish with certainty that a particular adverse event has been caused by the use of ephedra, based on the pattern of adverse event reports it has received and the scientific literature it has reviewed, FDA has concluded that ephedra poses a risk of cardiovascular and nervous system effects among consumers who are young to middle-aged.

The types of adverse events that we identified in the health-related call records from Metabolife International were consistent with the types of adverse events reported to FDA and with the documented physiological effects of ephedra. Although the call records contained limited information for most of the reports, we identified 14,684 call records that contained reports of at least one adverse event among consumers of Metabolife 356. Our count of 92 serious events—heart attacks, strokes, seizures, and deaths—was similar to that of other reviews of the call records, including counts by Metabolife International and its consultants. Many of the serious events were reported among relatively young consumers—more than one-third concerned consumers who reported an

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<sup>3</sup>U.S. General Accounting Office, *Dietary Supplements: Uncertainties in Analyses Underlying FDA's Proposed Rule on Ephedrine Alkaloids*, [GAO/HEHS/GGD-99-90](#) (Washington, D.C.: July 2, 1999); *Health Products for Seniors: "Anti-Aging" Products Pose Potential for Physical and Economic Harm*, [GAO-01-1129](#) (Washington, D.C.: Sept. 7, 2001); *Dietary Supplements for Weight Loss: Limited Federal Oversight Has Focused More on Marketing Than on Safety*, [GAO-02-985T](#) (Washington, D.C.: July 31, 2002); and *Dietary Supplements: Review of Health-Related Call Records for Users of Metabolife 356*, [GAO-03-494](#) (Washington, D.C.: Mar. 31, 2003).

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age under 30. In addition, for the call records containing information on the amount of product consumed or length of product use, we found that most of the reported serious adverse events occurred among consumers who followed the usage guidelines on the Metabolife 356 label—the consumers reported that they did not take more of the product or take it for a longer period than the company recommended.

As part of its oversight of dietary supplements, FDA has taken some actions specifically focused on dietary supplements containing ephedra. FDA has issued warnings to manufacturers that focus on improper product labeling, issued warnings to consumers, and issued a proposed rule in 1997 that, among other things, would require a health warning on the label of dietary supplements containing ephedra and prohibit a dietary supplement from containing both ephedrine alkaloids—the active ingredient in ephedra—and a stimulant. FDA subsequently banned the sale of certain classes of over-the-counter drugs containing ephedrine and related alkaloids in combination with an analgesic or stimulant. As the 1997 proposed rule has not been finalized, there is no rule prohibiting the marketing of dietary supplements with similar ingredients, and many dietary supplements with ephedra, such as Metabolife 356, also include caffeine or other stimulants. To receive comments on new evidence, FDA recently reopened the comment period for the proposed rule, and FDA reported to us that the agency is in the process of reviewing comments it has received and has not reached a decision regarding further action.

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## Background

Ephedra, the most widely used ingredient in dietary supplements for weight loss, is a powerful stimulant that can affect the nervous and cardiovascular systems. Adverse events among consumers of dietary supplements containing ephedra have been described in scientific literature and in detailed adverse event reports. Because of concerns about the risks of ephedra, medical organizations, states, and athletic associations have sought to reduce the use of dietary supplements containing ephedra.

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## FDA Oversight of Dietary Supplements under DSHEA

Under DSHEA, FDA regulates dietary supplements, including vitamins, minerals, herbs and other botanicals, amino acids, certain other dietary substances, and derivatives of these items. DSHEA requires that dietary supplement labels include a complete list of ingredients and the amount of

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each ingredient in the product.<sup>4</sup> Dietary supplements may not contain synthetic active ingredients that are sold in over-the-counter drugs and prescription medications and cannot be promoted as a treatment, prevention, or cure for a specific disease or condition.

Under DSHEA, manufacturers are responsible for ensuring the safety of dietary supplements they sell. Dietary supplements do not need approval from FDA before they are marketed; thus FDA generally addresses safety concerns only after dietary supplements are marketed. DSHEA does not require manufacturers to register with FDA,<sup>5</sup> identify the products they manufacture, or provide reports of adverse events to FDA. Mechanisms that FDA uses to oversee dietary supplements and other products it regulates differ (see app. I for more details).

Since manufacturers of dietary supplements are not required to provide reports of adverse events to FDA, the agency relies on voluntary postmarket reporting of adverse events to better understand the safety of dietary supplements. Some individual adverse event reports are especially valuable to FDA because they include enough information to help FDA determine if the adverse event was likely caused by the supplement. These reports include information about the receipt of medical care, health care professionals' attribution of adverse events to the consumption of dietary supplements, the consumer's appropriate use of the products, the consumer's use of other products, underlying health conditions and other alternative explanations for the adverse event, and the consistency of symptoms with the documented effects of the dietary supplement.

FDA, through the Department of Justice, can take enforcement action in court against dietary supplements that are adulterated to remove them

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<sup>4</sup>Products may include "proprietary blends," which must list all ingredients but do not need to list the amount of each ingredient.

<sup>5</sup>However, manufacturers and distributors of dietary supplements are required to register with FDA no later than December 13, 2003, under the Public Health Security and Bioterrorism Preparedness and Response Act of 2002, Pub. L. No. 107-188, 116 Stat. 594. FDA issued a proposed rule in February 2003 to implement the requirement. *See 68 Fed. Reg.* 5378 (Feb. 3, 2003).

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from the market.<sup>6</sup> A dietary supplement is considered adulterated under a number of circumstances, including when it

- presents a “significant or unreasonable risk of illness or injury” under the conditions of use recommended or suggested in its labeling, or under ordinary conditions of use if there are no suggestions or recommendations in the labeling, or
- bears or contains any “poisonous or deleterious substance” which may render it injurious to health under the conditions of use recommended or suggested in its labeling.

Instead of going to court, FDA may choose to take administrative action to prohibit the sale of dietary supplements it considers to be adulterated. FDA can promulgate a regulation declaring a particular dietary supplement to be adulterated. FDA has not taken this action with any dietary supplement. FDA can also issue an advisory letter explaining why it considers the dietary supplement to be adulterated. The advisory letter provides guidance to the industry regarding FDA’s opinion and notifies the public that FDA may take legal action against firms or individuals that do not follow the letter’s advice. FDA has done this for two dietary supplement ingredients, comfrey and aristolochic acid.

In addition, although it has never been done, the Secretary of Health and Human Services (HHS) may declare that a dietary supplement is adulterated because it poses an “imminent hazard” to public health or safety. In doing so, the Secretary must initiate an administrative hearing to affirm or withdraw the declaration.

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## Health Concerns about Ephedra

Ephedra has been associated with numerous adverse health effects. As we previously reported,<sup>7</sup> case reports and scientific literature have suggested that ephedrine alkaloids can increase blood pressure in those with normal blood pressure, predispose certain individuals to rapid heart rate, and cause stroke, among other things. We also reported descriptions of adverse events associated with ephedrine alkaloids that affected the central nervous system, such as seizures, mania, and paranoid psychoses.

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<sup>6</sup>“Adulterated” is the statutory term used to describe dietary supplements and other FDA-regulated products that are unsuitable for marketing. It is illegal to market any adulterated product.

<sup>7</sup>[GAO/HEHS/GGD-99-90](#).

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FDA has received reports of adverse events associated with dietary supplements containing ephedra, including heart attack, stroke, seizure, psychosis, and death, that are consistent with the scientific literature. In February 2003, the RAND Corporation released a review of the scientific evidence on the safety and efficacy of dietary supplements containing ephedra<sup>8</sup> and concluded that a sufficient number of cases of these same types of events had occurred in young adults to warrant further scientific study of the causal relationship between ephedra and these serious adverse events. RAND also found that use of ephedra or ephedrine plus caffeine is associated with a number of other adverse effects, including an increased risk of nausea, vomiting, heart palpitations, and psychiatric symptoms such as anxiety and change in mood.

Because of these health concerns, many organizations and jurisdictions have taken actions aimed at reducing the use of dietary supplements containing ephedra. The American Medical Association and the American Heart Association have urged FDA to ban the sale of dietary supplements containing ephedra. In January 2002, Health Canada issued a Health Advisory for Canadians not to use certain products containing ephedra, especially those that also contain caffeine and other stimulants. In 2003, Illinois banned the sale of products containing ephedra and other states have similar bans under consideration. In addition, some states have banned the sale of such products to minors or required label warnings. Several sports organizations, including the NCAA, the National Football League, the U.S. Olympic Committee, and the International Olympic Committee, have banned the use of ephedra by their athletes.

In 2003, General Nutrition Centers, the nation's largest specialty retailer of nutritional supplements, discontinued the sale of products containing ephedra, as have three other major retail outlets. Some manufacturers have stopped producing dietary supplements containing ephedra. Other

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<sup>8</sup>Paul Shekelle, et al., *Ephedra and Ephedrine for Weight Loss and Athletic Performance Enhancement: Clinical Efficacy and Side Effects*. Evidence Report/Technology Assessment No. 76 (prepared by Southern California Evidence-based Practice Center, RAND, under Contract No. 290-97-0001, Task Order No. 9). AHRQ Publication No. 03-E022 (Rockville, Md.: Agency for Healthcare Research and Quality, February 2003).



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manufacturers continue to offer dietary supplements containing ephedra while also offering similar products that are ephedra-free.<sup>9</sup>

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## Adverse Event Reports Have Led FDA to Conclude That Dietary Supplements Containing Ephedra Pose a Significant Public Health Hazard

Using the adverse event reports it has received and evidence from the scientific literature, FDA has concluded that dietary supplements containing ephedra pose a “significant public health hazard.” FDA and others have received thousands of reports of adverse events among users of dietary supplements containing ephedra, more than for any other dietary supplement ingredient. Metabolife International also received thousands of reports of adverse events.

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## More Adverse Events Have Been Reported for Products Containing Ephedra Than for Any Other Dietary Supplement

FDA has received more reports of adverse events for dietary supplements containing ephedra than for any other dietary supplement ingredient. In addition, poison control centers and one manufacturer, Metabolife International, have received thousands of reports of adverse events associated with dietary supplements containing ephedra. From February 22, 1993, through July 14, 2003, FDA received 2,277 reports of adverse events associated with dietary supplements containing ephedra, which was 15 times more reports than it received for the next most commonly reported herbal dietary supplement, St. John’s wort.<sup>10</sup>

Other organizations also have received a large number of adverse event reports for dietary supplements containing ephedra. The American Association of Poison Control Centers received 1,428 reports of adverse events associated with dietary supplements containing ephedra, either alone or in combination with other botanical dietary supplement

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<sup>9</sup>Some ephedra-free products include other herbal stimulants, such as *Citrus aurantium*. *Citrus aurantium* contains synephrine, which is chemically similar to the ephedrine and pseudoephedrine found in many over-the-counter and allergy medicines and in dietary supplements containing ephedra.

<sup>10</sup>In total, FDA received 5,574 adverse reports for dietary supplements during that period. The total number of reports of adverse events for ephedra products includes 135 reports from the Metabolife International call records that FDA designated as serious adverse events.

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ingredients, in 2002,<sup>11</sup> nearly two-thirds as many as FDA received over a 10-year period. The centers noted that there were more reports of adverse events for ephedra-containing dietary supplements than for others. Further, as we reported in March 2003, Metabolife International had 14,684 health-related call records that contained reports of adverse events associated with its product, Metabolife 356, from May 1997 through July 2002.<sup>12</sup> Neither the American Association of Poison Control Centers nor Metabolife International is required to report these adverse events to FDA.

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### FDA Has Determined That the Adverse Event Reports and Scientific Literature Indicate That Dietary Supplements Containing Ephedra Pose a Significant Public Health Hazard

From the adverse event reports it has received and the scientific literature it has reviewed, FDA concluded in March 2000 that dietary supplements containing ephedra pose a significant public health hazard that primarily involves consumers who are young to middle-aged and can result in adverse cardiovascular and nervous system effects.<sup>13</sup> It further concluded that many of the adverse events were serious, resulting in morbidity and mortality that would not be expected in a young population and that could further compromise the health of more vulnerable older adults or those with underlying conditions.

A study commissioned by FDA estimated that the agency receives reports for less than 1 percent of adverse events associated with dietary supplements.<sup>14</sup> Although causality cannot be determined based on the individual adverse event reports FDA receives, the agency uses these reports to identify possible risks to consumers from dietary supplements. As we have previously reported, there are well-known weaknesses in the current system of voluntary reporting of adverse events, such as different interpretations in determining an adverse event, underreporting,

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<sup>11</sup>William A. Watson, et al., "2002 Annual Report of the American Association of Poison Control Centers Toxic Exposure Surveillance System," *American Journal of Emergency Medicine* (in press). See also Stephen Bent, et al., "The Relative Safety of Ephedra Compared with Other Herbal Products," *Annals of Internal Medicine*, vol. 138 (2003), 468-471.

<sup>12</sup>[GAO-03-494](#).

<sup>13</sup>Food and Drug Administration, *Assessment of Public Health Risks Associated with the Use of Ephedrine Alkaloid-containing Dietary Supplements* (Mar. 31, 2000) (Docket No. 00N-1200).

<sup>14</sup>U.S. Department of Health and Human Services, Office of Inspector General, *Adverse Event Reporting for Dietary Supplements: An Inadequate Safety Valve*, OEI-01-00-00180 (Washington, D.C.: Apr. 2001).

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difficulties estimating population exposure, and poor report quality.<sup>15</sup> Despite these limitations, FDA maintains that even isolated reports can be definitive in associating products with an adverse effect if the report contains sufficient evidence, such as supporting medical documents, a temporal relationship between the product and effect, and evidence of dechallenge and rechallenge.<sup>16</sup>

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## Metabolife International Call Records Contain Reports of Adverse Events That Are Consistent with the Types of Adverse Events Reported to FDA

The types of adverse events that we identified in the Metabolife International call records are consistent with the types of adverse events reported to FDA and with the documented physiological effects of ephedra. As we recently reported, most of the Metabolife International call records contained limited information about the event and the consumer. Nonetheless, the call records contribute to existing knowledge about adverse events that have been associated with ephedra use. In our review, we identified 14,684 call records that contained reports of at least one adverse event among consumers of Metabolife 356. Within these call records, we found 92 reports of serious adverse events—heart attacks, strokes, seizures, and deaths—a count that was similar to that of other reviews of the call records. In addition, the call records contain reports of serious adverse events in consumers who were young and among those who used the product within the recommended guidelines. These findings are consistent with reports FDA has received regarding dietary supplements containing ephedra.

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## Consumer Information in the Metabolife International Call Records Was Limited

In our review of health-related call records for users of Metabolife 356,<sup>17</sup> we found that the information in the call records was limited. Call records were sometimes difficult to read and interpret, and consumer information was not consistently recorded. In some cases, the evidence for a report of an adverse event was limited to a single word on a call record. In other cases, information was entered into a form developed by Metabolife International with multiple boxes for consumer- and event-related information. Most call records did not document complete information about the consumer's age, sex, weight, and height. Because the company

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<sup>15</sup>[GAO/HEHS/GGD-99-90](#).

<sup>16</sup>Dechallenge is evident when signs and symptoms resolve or improve when a consumer stops using a product, and rechallenge is evident when symptoms recur when the consumer resumes using the product.

<sup>17</sup>[GAO-03-494](#).

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did not systematically follow up on calls reporting adverse events, and the adverse events were not reported to FDA, it is not possible to gather more complete information or medical records.

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## Metabolife International Call Records Contained Reports of Thousands of Adverse Events, Some of Which Were Serious, among Consumers of Metabolife 356

As we reported in March 2003, we identified 14,684 call records that contained at least one report of an adverse event among consumers of Metabolife 356.<sup>18</sup> The types of reported adverse events were consistent with the cardiovascular and central nervous system effects that have been associated with ephedra products in the literature, adverse event reports received by FDA, other case reports, and RAND's review. Within the call records, we identified 92 reports of heart attack, stroke, seizure, and death (see table 1).<sup>19</sup> Our count of reports of these serious adverse events was similar to that of other reviews of the Metabolife International call records, including counts by Metabolife International and its consultants.<sup>20</sup>

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**Table 1: Number of Reports of Heart Attack, Stroke, Seizure, or Death in Metabolife International Call Records**

Type of adverse event	Number <sup>a</sup>
Heart attack	18
Stroke	26
Seizure	43
Death	5

Source: Metabolife International.

Note: GAO analysis of 14,684 health-related call records provided by Metabolife International.

<sup>a</sup>The counts do not represent unique consumers because a single call record may have more than one complaint and because some consumers called the Metabolife health information phone line more than once.

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<sup>18</sup>A single call record may have had more than one complaint.

<sup>19</sup>We highlighted these serious adverse events because they are identified in FDA's proposed label warning for dietary supplements containing ephedra. *See 68 Fed. Reg. 10417 (Mar. 5, 2003)*.

<sup>20</sup>Metabolife International has not issued a report on its review of the call records, but provided us with a list of the calls it believed to report heart attack, stroke, seizure, and death. Metabolife International also commissioned reviews by three consultants (see [GAO-03-494](#)).

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We also found 1,079 reports of other types of adverse events that FDA identified as serious or potentially serious.<sup>21</sup> These included chest pain, significant elevations in blood pressure, systemic rash, and urinary infection. In addition to these 1,079 reports, we found records that contained reports of a broad range of other types of adverse events, including changes in heart rate such as palpitations and increased heart rate; blood in stool; blood in urine; bruising; hair loss; and menstrual irregularity.<sup>22</sup>

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### Reports of Serious Adverse Events Involved Consumers Who Were Relatively Young

Within the subset of call records that contained information on age, the distribution of ages suggests that a relatively young population was experiencing the reported serious adverse events. Among the call records that contained a report of a serious event, 44 percent included information on age.<sup>23</sup> For these call records, more than one-third concerned consumers who reported an age under 30—the average reported age was 38 (ranging from 17 to 65). As noted above, FDA has also received reports of serious adverse events occurring in a population of young adults. Because we do not know the age profile of all Metabolife 356 consumers, we cannot determine if the age distribution among those reporting serious adverse events in the Metabolife International call records reflects that age profile.

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<sup>21</sup>In its 1997 proposed rule on dietary supplements containing ephedra, FDA identified as serious or potentially serious some types of adverse events for which the agency had received reports. *See* 62 *Fed. Reg.* 30678 (June 4, 1997).

<sup>22</sup>Within the complete set of call records, we also found 332 reports of visits to either an emergency department or a hospital. According to FDA officials, unlike most adverse events related to foods, adverse event reports it had received related to ephedra products commonly involved a visit to a physician or an emergency room. FDA considers a hospitalization or prolongation of an existing hospitalization to be a serious adverse event. Metabolife International records did not consistently distinguish between an actual hospitalization and “going to the hospital,” which may not have resulted in an actual hospitalization.

<sup>23</sup>For the entire set of the Metabolife International call records, 42 percent contained information on the age of the consumer.

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## Serious Adverse Events Were Reported among Consumers Who Used Metabolife 356 within Recommended Guidelines

Within the subset of Metabolife International call records that contained information on how the product was used by the consumer, most of the reported serious adverse events occurred among consumers who reported using the product within the guidelines on the Metabolife 356 label—that is, who reported that they did not take more of the product or take it for a longer period than recommended.<sup>24</sup> Information about product use, however, was incomplete—40 and 55 percent of the call records that reported a serious event contained information about the amount of Metabolife 356 used and the duration of use, respectively. Among the call records that reported a serious adverse event and also contained information about product use, 97 percent of consumers reported using an amount of product within the recommended guidelines. Similarly, 71 percent of those consumers reported using the product for a length of time that was within the recommended guidelines.<sup>25</sup> This pattern is consistent with findings from FDA’s review of adverse events associated with ephedra products.<sup>26</sup>

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## FDA Has Taken Some Actions to Oversee Dietary Supplements Containing Ephedra

As part of its oversight of dietary supplements, FDA has taken some actions specifically focused on dietary supplements containing ephedra. FDA has issued warnings that focus on improper product labeling, issued warnings to consumers, and issued a proposed rule in 1997 that, among other things, would require a health warning on the label of dietary supplements containing ephedra and prohibit a dietary supplement from containing both ephedra and a stimulant. However, parts of this rule remain under consideration 6 years after it was first proposed.

As we previously reported, FDA has focused its enforcement actions regarding dietary supplements on improper labeling.<sup>27</sup> For example, in February 2003, FDA issued warning letters to 26 firms that sell dietary

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<sup>24</sup>The product label recommends that adults take one to two caplets two to three times per day or every 4 hours, not to exceed eight caplets per day. The label also recommends that persons should not use the product for more than 12 weeks and that exceeding the recommended amount may cause serious adverse health effects, including heart attack or stroke.

<sup>25</sup>For all call records containing information on the amount of product used or duration of use, 99 and 91 percent of consumers, respectively, reported using the product within the guidelines recommended on the label.

<sup>26</sup>Food and Drug Administration, March 2000.

<sup>27</sup>[GAO-02-985T](#).

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supplements containing ephedra. All of these letters advised marketers that label claims for enhancement of physical performance were unsubstantiated and the products were therefore misbranded.

FDA and HHS have also directly warned consumers about the safety of dietary supplements containing ephedra. In February 1995, FDA issued a press release warning consumers about a specific dietary supplement product that contained both ephedra and caffeine, because it had determined that the product represented a threat to public health. Further, in February 2003, the Secretary of HHS issued a statement to caution people against using dietary supplements containing ephedra and indicated that FDA continues to have serious concerns about the risks of these dietary supplements.

FDA has also taken actions in its oversight of dietary supplements in general. Specifically, FDA has conducted facility inspections<sup>28</sup> and proposed good manufacturing practice (GMP) regulations<sup>29</sup> that focus on product quality in general, not the safety of an individual ingredient.

FDA first issued a proposed rule to regulate dietary supplements containing ephedrine alkaloids in 1997.<sup>30</sup> The proposed rule would

- define the amount of ephedrine alkaloids in a serving of dietary supplement at and above which the product would be deemed adulterated (8 milligrams),
- establish labeling requirements regarding maximum frequency of use and daily serving limits,
- require that labels on these supplements contain a statement warning that the product should not be used for more than 7 days,
- prohibit the use of ephedrine alkaloids with ingredients that have a known stimulant effect (e.g., caffeine),

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<sup>28</sup>Since 1999, FDA, its state partners, and state contractors have inspected 6 percent of the known dietary supplement manufacturing and repacking facilities annually. Inspections focus on sanitation, buildings and facilities, equipment, production, and process controls.

<sup>29</sup>In March 2003, FDA issued proposed GMP regulations for dietary ingredients and dietary supplements. *See* 68 *Fed. Reg.* 12158 (Mar. 13, 2003). The comment period for the proposed GMPs was extended until Aug. 11, 2003. *See* 68 *Fed. Reg.* 27008 (May 19, 2003). GMP regulations are important in ensuring that the product is not contaminated and contains what the label reports. They do not, however, address the safety of any individual ingredient, such as ephedra.

<sup>30</sup>62 *Fed. Reg.* 30678 (June 4, 1997).

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- prohibit labeling claims that promote long-term intake of the supplements to achieve the purported purpose,
  - require a warning statement in conjunction with claims that encourage short-term excessive intake to enhance the purported effect, and
  - require that specific warning statements appear on product labels.

Our 1999 report on the proposed rule was critical of the science FDA used to support the serving size and duration of use limits in the proposed rule.<sup>31</sup> However, we did not conclude that dietary supplements containing ephedra were safe, and we commented that the adverse events reported to FDA were serious enough to warrant FDA's further investigation of ephedra safety. Primarily, we were concerned that FDA used only 13 adverse event reports to establish serving limits and had weak support for proposed limits on duration of use. Partly as a result of our review, FDA withdrew the sections of the proposed rule on serving size and duration of use limits.<sup>32</sup>

In the interim, FDA has taken action to regulate certain drugs that contain ephedrine, the active ingredient in ephedra. In September 2001, FDA issued a final rule stating that certain over-the-counter drugs containing ephedrine and related alkaloids in combination with an analgesic or stimulant could not be marketed as over-the-counter drugs.<sup>33</sup> There currently is no similar rule prohibiting the marketing of dietary supplements containing ephedra in combination with analgesics or stimulants, such as caffeine. As a result, dietary supplements may contain ingredients that are prohibited in drugs. In fact, many dietary supplements with ephedra, such as Metabolife 356, also include caffeine. The proposed rule contains a provision that would prohibit dietary supplements from containing both ephedra and other stimulants.

In March 2003, almost 6 years after the initial proposal, FDA reopened the comment period for the remaining provisions of this proposed rule for 30 days.<sup>34</sup> FDA sought comments on three areas:

- New evidence on health risks associated with ephedra.

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<sup>31</sup> [GAO/HEHS/GGD-99-90](#).

<sup>32</sup> 65 *Fed. Reg.* 17474 (Apr. 3, 2000).

<sup>33</sup> See 66 *Fed. Reg.* 49276 (Sept. 27, 2001).

<sup>34</sup> 68 *Fed. Reg.* 10417 (Mar. 5, 2003).



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- Whether the currently available evidence and medical literature demonstrate that dietary supplements containing ephedra pose a “significant or unreasonable risk of illness or injury” under the conditions of use recommended or suggested in their labeling, or under ordinary conditions of use if there are no suggestions in the labeling.
  - A new warning label for ephedra products that warns about reports of serious adverse events after the use of ephedra, including heart attack, seizure, stroke, and death; cautions that the risk can increase with the dose, with strenuous exercise, and with other stimulants such as caffeine; specifies certain groups (such as women who are pregnant or breast feeding and persons under 18) who should not use these products; and lists other diseases, such as heart disease and high blood pressure, that should rule out the use of ephedrine alkaloids.

On July 14, 2003, FDA reported to us that the agency is in the process of reviewing the comments and has not reached a decision regarding further action. While FDA has not attempted to ban the marketing of dietary supplements containing ephedra, the agency has sought, in these comments, additional information that would help it determine whether or not such action would be warranted.

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## Concluding Observations

Because the regulatory framework for dietary supplements is primarily a postmarketing program and FDA does not review the safety of dietary supplements before they are marketed, adverse event reports are important sources of information about the health risks of dietary supplements containing ephedra. It is often difficult to demonstrate conclusively that a single reported adverse event was caused by ephedra, but some individual reports, particularly when they are complemented by follow-up investigation of the case, can be especially informative. Although the information in the Metabolife International call records we examined was limited, the types of adverse events we observed were consistent with the known risks of ephedra, including serious events such as five reports of death. Based on the pattern of adverse event reports FDA has received and the consistency of those reports with the known effects of ephedra from the scientific literature, the agency concluded 3 years ago that dietary supplements containing ephedra pose a “significant public health hazard.” FDA is currently reviewing information that will help the agency determine what further actions are warranted.

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Mr. Chairman, this completes my prepared statement. I would be happy to respond to any questions you or other Members of the Subcommittee may have at this time.

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## Contact and Acknowledgments

For more information regarding this testimony, please call Marcia Crosse at (202) 512-7119. Key contributors include Martin T. Gahart, Carolyn Feis Korman, Chad Davenport, Roseanne Price, and Julian Klazkin.

# Appendix I: Mechanisms for FDA Oversight of Different Types of Products

Product class	Product registration	Manufacturer registration	Premarket approval of products	Specific good manufacturing practices	Voluntary postmarket adverse event reporting system	Mandatory manufacturer reporting of adverse events	Safety-related labeling requirements
Dietary supplements		X <sup>a</sup>		Proposed in 2003 <sup>b</sup>	X		Some
Conventional foods		X <sup>a</sup>		X	X <sup>c</sup>		Some
Food additives		X <sup>a</sup>	X	X	X		X
Monograph drugs <sup>d</sup>	X	X		X	X		X
New Drug Application drugs <sup>e</sup>	X	X	X	X	X	X	X
Infant formula	X	X		Proposed in 1996 <sup>f</sup>	X	X	X

Source: GAO analysis of U.S. Department of Health and Human Services, Office of Inspector General, *Adverse Event Reporting for Dietary Supplements: An Inadequate Safety Valve*.

<sup>a</sup>Under the Public Health Security and Bioterrorism Preparedness and Response Act of 2002, Pub.L. No. 107-188, 116 Stat. 594, manufacturers and distributors are required to be registered with FDA no later than December 13, 2003.

<sup>b</sup>FDA proposed good manufacturing practices in March 2003. Comments are due to FDA by August 11, 2003. Regulations regarding the packaging of dietary supplements containing iron were issued in 1997.

<sup>c</sup>FDA does not collect or evaluate all adverse event reports on all conventional food. In addition, excluded from this system are the investigations FDA conducts following food-borne illness outbreaks.

<sup>d</sup>Monograph drugs are typically over-the-counter drugs that must adhere to specific safety standards set for each ingredient and do not undergo clinical testing.

<sup>e</sup>New Drug Applications must be submitted to FDA for all prescription drugs and some over-the-counter drugs prior to marketing. This application must include data that demonstrate the safety and efficacy of the product.

<sup>f</sup>The comment period for the proposed good manufacturing practices regulation was reopened in June 2003, and closes August 26, 2003.

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