Chapter 3. Results

Results of Literature Search

Efficacy Analysis

Figure 8 displays the flow of the literature review. As a result of computerized library searches, reference mining, talking to experts, and searching government files (see Methods), we ordered 550 articles. Of those 550, we were unable to obtain 20 articles, mostly foreign or very old background articles, none of which appeared (from their titles and keywords) to be clinical trials of ephedrine or ephedra.

Of the 530 articles collected, 59 reported results from randomized clinical trials or controlled clinical trials that assessed the effects of either ephedrine or herbal ephedra on weight loss or athletic performance. The 59 articles, which corresponded to 52 unique controlled clinical trials, went on to further review and data abstraction. Articles that did not go on to initial data abstraction included 71 case reports or case series articles that reported adverse events. One hundred forty-nine articles were rejected from further review for "topic:" These articles did not discuss ephedra or ephedrine, although they may have discussed phenylpropanolamine, pseudoephedrine, or caffeine, or provided general background on herbal medicine, weight loss, or athletic performance enhancement. One hundred one other articles were rejected for "subject." They discussed use of ephedra or ephedrine for other purposes, such as bronchial or cold medication. Sixty-eight more were rejected for "population." Nearly all were animal studies. Another four articles were not actually articles but government documents or public testimony, and three other articles were duplicates of articles already on file. Seventy-five additional articles were rejected for design, including previous reviews of ephedra or ephedrine, descriptions of its chemical properties, editorials, commentaries, letters to journal editors that did not report new cases, and newspaper or trade journal stories.

Adverse Events Analysis

The adverse events analysis includes 52 controlled trials and 65 of the 71 case reports/case series articles (six articles were rejected because they were duplicates of articles or reports already included in the analysis).

Efficacy

Weight Loss

Of the 52 unique controlled trials that assessed the effects of either synthetic ephedrine or herbal ephedra on weight loss or athletic performance, 44 of those assessed the effects of ephedra, ephedrine, or ephedrine and other compounds on weight loss. Of these 44 trials, 18 were excluded from pooled analysis because they had treatment duration of less than eight weeks (the longest published weight loss intervention was six months, and no studies assessed post-intervention weight maintenance). Six more trials were excluded for a variety of reasons (See Table 9). We classified the comparisons made in the remaining 20 trials into six categories:

1. Ephedrine versus placebo
2. Ephedrine plus caffeine versus placebo
3. Ephedrine plus caffeine versus ephedrine alone
4. Ephedrine versus another active pharmaceutical for weight loss
5. Ephedra versus placebo
6. Ephedra plus herbs containing caffeine versus placebo

For the 16 trials that reported baseline sample sizes, the attrition rate in the treatment arms averaged 27 percent, whereas the attrition rate in the placebo arms averaged 29 percent. This difference was not statistically significant. Five trials reported more dropouts from the treatment than from the placebo group: Four of these trials reported a statistically significant benefit for the treatment, and one did not. Eight trials reported more dropouts from the placebo group than the treatment group. Five of these trials reported a statistically significant benefit for treatment, whereas three did not. Three trials reported an equivalent number of dropouts from the treatment and placebo groups. No significant association was found between the frequency of favorable results and the relative proportion of dropouts in the treatment and placebo groups.

Ephedrine Versus Placebo

We identified five trials (which contained six comparisons) that assessed the effect of ephedrine versus placebo.[84-86, 88, 94] A study by Pasquali had two comparison arms that assessed different doses.[85] The scores on Jadad's scale (0-5) for these trials were 1, 2, 2, 3, and 3, respectively. All five were described as randomized, placebo-controlled trials. Three of the trials (with four comparisons) reported results at three months, and three of the trials reported results at four months. The random effects pooled estimate of the rate of weight loss per month was an effect size of -0.50 (95% CI: -0.85, -0.15), which translates to a monthly weight loss of 1.3 pounds more than weight lost on placebo (Table 10 and Figure 9). The pooled average percent weight loss in the ephedrine-treated patients, compared to pretreatment weight, was 11 percent at 4 months.

A sensitivity analysis on only those trials that scored three or higher on the Jadad scale yielded a pooled estimate of effect substantially lower than the main analysis (effect size = -0.20); this difference was statistically significant ($p = 0.049$). All of these trials had an attrition rate greater than 20 percent; therefore, no sensitivity analysis on attrition could be performed. A final sensitivity analysis, in which the trial by Moheb[84] was dropped, did not materially change these results.

In our dose analysis, only high doses of ephedrine resulted in a weight loss that was significantly greater than zero, and the difference in weight loss between medium dose trials and high dose trials approached statistical significance ($p = 0.052$). Neither graphical nor statistical tests yielded evidence of publication bias (See Table 11 and Figure 10).

We interpret these data to indicate that the use of ephedrine is associated with a statistically significant increase in weight loss (1.3 pounds of weight loss per month) compared with that of placebo for up to four months of use.

Ephedrine plus caffeine versus placebo

We identified 12 trials that assessed the effect of ephedrine plus caffeine versus placebo for weight loss.[84, 86-88, 90-92, 95, 96, 103, 111, 112] Six trials [86, 87, 92, 95, 96, 112] had scores of three or greater on the Jadad scale, a threshold that in other settings has been associated with less bias.[83] Seven were described as randomized, double blind, placebo-controlled trials. Four of the trials measured weight loss at two months, four trials measured it at three months, and five trials measured it at four months. The random effects pooled estimate of the rate of weight loss per month was an effect size of -0.85 (95% CI: -1.1, -0.61), which translates to a weight loss of 2.2 pounds per month above that with placebo (Table 11 and Figure 11). The pooled average percent weight loss in the ephedrine plus caffeine treated patients, compared to pretreatment weight, was 11 percent at 4 months.

A sensitivity analysis on only those trials that scored three or greater on the Jadad score yielded a result similar to the main analysis. Another sensitivity analysis on only those trials that had less than 20 percent attrition yielded a similar pooled estimate effect size of -0.74 (95% CI: -1.2, -0.3). Two trials[96, 112] in this category were randomized, double-blind, placebo-controlled trials with an attrition rate of less than 20 percent. The first[112] reported an effect somewhat greater than the main analysis (effect size = -1.35; 95% CI: -2.2, 0.54). The second[96] had a smaller effect (effect size = -0.46; 95% CI: -1.3, 0.34). A fourth sensitivity analysis in which the trial by Moheb[84] was dropped did not change the result compared with the primary analysis, nor did sensitivity analyses that dropped trials that also included synephrine or aspirin.

In our dose analysis, there was a trend toward increased weight loss with higher doses (weight loss greater than placebo of 2.0, 2.2, and 2.6 pounds per month for low, medium, and high doses, respectively) but these differences were not statistically significant. Neither visual nor graphical tests revealed any evidence of publication bias (See Table 11 and Figure 12).

We interpret these data to indicate that the use of the combination of ephedrine and caffeine is associated with a significantly greater (2.2 pound) weight loss per month than is associated with placebo, for up to four months duration.

Ephedrine plus caffeine versus ephedrine

We identified three trials that included arms that compared a combination of ephedrine and caffeine to ephedrine alone.[84, 86, 88] The Jadad scores for these trials were 1, 2, and 3 respectively, and all three had attrition rates of greater than 20 percent. The random effects pooled estimate of the rate of weight loss per month was -0.31 (95% CI: -0.60, -0.02), which equates to a weight loss of 0.8 pounds per month more than with ephedrine alone (Table 13 and Figure 13). There were too few trials to perform any sensitivity analysis.

We interpret these data to indicate that addition of caffeine to ephedrine is associated with a statistically significant increase in weight loss per month of about 0.8 pounds, over that attributable to ephedrine alone.

Ephedrine versus another active weight loss therapy

We identified two trials that compared ephedrine with another active weight loss therapy (Table 14). The trials, both Danish, are briefly described here. In 1994, Breum and colleagues[113]

published the results of a randomized controlled trial comparing the effect of dexfenfluramine to a combination of ephedrine and caffeine. At 15 weeks, the dexfenfluramine group had lost an average of 6.9 kg (15.2 lb.), whereas the ephedrine and caffeine group had lost 8.3 kg (18.3 lb.), a difference that was not statistically significant. The other Danish study,[87] published in 1981, compared the effects of the Elsinore pill (a prescription that contained ephedrine and caffeine) with those of diethylpropion. At 12 weeks, the diethylpropion patients had a median weight loss of 8.4 kg (18.5 lb.), while those taking Elsinore pills lost a median of 8.1 kg (17.8 lb.), a difference that was not significant. Each of these two trials[87] included approximately 40 ephedrine and 40 other treatment patients. The approximate weight loss in the ephedrine groups was 8.4 kg (± approximately 4.0 kg SD) (18.4 ± 8.8 lb.) over three months. Based on a two-sided test of significance level 0.05 and assuming the same variance in both groups, trials of this size have only 59 percent power to distinguish between an 8.4 kg weight loss in the ephedrine group and a 6.4 kg (14.1 lb.) weight loss in the active treatment group, i.e. a difference of 30% between the groups. In order to attain 80 percent power, a study would need 67 ephedrine patients and 67 comparison treatment patients.

Ephedra versus placebo

We identified a single trial that assessed the effect of herbal ephedra versus placebo.[114] This trial was described as a randomized, double-blind, parallel group assessment of Metab-O-Lite, a dietary supplement that contains ephedra and other compounds but does not contain caffeine or herbs that contain caffeine. The duration of the trial was three months. Those in the ephedra arm lost 1.8 pounds more per month than did those in the placebo arm (95% CI: -2.7, -1.0) (Table 15). This trial scored four on Jadad's scale and had 17 percent attrition.

Ephedra plus herbs containing caffeine versus placebo

We identified four trials that assessed the effect of herbal ephedra plus herbs containing caffeine versus placebo.[89, 93, 115, 116] The Jadad scores for these four trials were 5, 5, 2, and 2 respectively; and all four were described as randomized placebo-controlled trials. Two of the trials reported outcomes at two months, one trial reported three-month outcomes, and one trial reported four-month results. The pooled random effects estimate of the rate of weight loss per month of these four trials was -0.81 (95% CI, -1.12, -0.51), which equates to a weight loss of 2.1 pounds per month more than that for placebo, for up to four months (Table 16 and Figure 14). The pooled average percent weight loss in the ephedra-treated patients, compared to pretreatment weight, was 5.2 percent at four months. A sensitivity analysis for only those trials that scored three or more on the Jadad scale yielded a result similar to the main analysis. All studies assessed medium doses of ephedra; therefore no analysis of dose effect was possible. Neither visual nor graphical tests revealed any evidence of publication bias (Table 11 and Figure 15).

We interpret these data to indicate that the use of a combination of ephedra plus herbs containing caffeine is associated with a statistically significant increase in weight loss per month of 2.1 pounds compared with that of placebo, for up to four months duration.

Meta-regression analysis

In order to assess the effects of ephedrine, ephedrine plus caffeine, and ephedra plus herbs containing caffeine on weight loss, we conducted a meta-regression analysis. The results are displayed in Table 17 and Figure 16. The table shows the pooled monthly weight loss in pounds

and its confidence interval for each comparison group versus placebo. All are significantly different from zero, indicating that all treatments are associated with an increased weight loss as compared to placebo. The last column, which compares ephedrine alone, ephedrine plus caffeine, and ephedra plus herbs containing caffeine, shows no significant differences among these treatments. Figure 16 lists the comparison groups in order of least effective versus placebo (left) to most effective (right). The individual effect sizes converted to pounds within each comparison are plotted vertically as circles, with the circle area inversely proportional to trial variance. We connect the pooled-effect sizes in pounds within each comparison group by line segments, showing the visible downward trend from left to right.

These data indicate that both ephedrine plus caffeine and ephedra plus herbs containing caffeine are somewhat more effective than ephedrine alone in promoting weight loss and that there is no difference in effect between ephedrine plus caffeine and ephedra plus herbs containing caffeine. To help put these data in context, we note that placebo-controlled trials of some FDA-approved weight loss pharmacotherapies have shown losses of 6-10 pounds more than placebo, over 6-12 months, for patients taking sibutramine[117-120] or orlistat;[121-125] or 16 pounds more than placebo, at 9 months, for patients taking phentermine.[126]

Athletic Performance

We found eight published controlled trials of the effects of synthetic ephedrine on athletic performance; most were crossover designs, and all but one also included caffeine. One trial,[127] which assessed the effect of ephedrine and exercise training on basal metabolic rate but did not report athletic performance outcomes, is not described below. The remaining seven trials were not appropriate for pooled analysis because they included various types of exercise and outcome measures. Thus, they are discussed here individually. We found no trials of the effect of herbal ephedra on athletic performance.

Six trials by Bell and colleagues assessed the exercise capacity of small groups of healthy males (all trials included 24 subjects or fewer). In their first trial,[128] healthy subjects who were not athletically trained were divided into four treatment groups: caffeine, ephedrine, ephedrine plus caffeine, and placebo. Outcome measures included oxygen consumption (VO_2), carbon dioxide production (VCO_2), and peak time to exhaustion. Ephedrine plus caffeine was reported to improve parameters of exercise performance such as oxygen consumption, time to exhaustion or carbon dioxide production by 20 to 30 percent, but neither caffeine nor ephedrine alone had significant effects. A follow up trial,[129] using a similar population and outcome measures but a lower dose of caffeine and ephedrine, showed similar effects on exercise performance and fewer side effects. Nausea and vomiting were reported in a third of subjects given 1 mg/kg ephedrine with 5 mg/kg caffeine, but none of the subjects given a lower dose (0.8 mg/kg ephedrine and 4 mg/kg caffeine) experienced symptoms. A third trial[130] assessed the effects, in a field trial, of ephedrine plus caffeine on VO_2 and time to complete a standardized exercise test, and again reported improvements in the group treated with ephedrine plus caffeine. A fourth trial[131] tested the effects of ephedrine plus caffeine on body temperature regulation and oxygen consumption during sub-maximal exercise in a hot environment and found that the combination did not increase body temperature significantly. A fifth trial[132] compared the effects of placebo, caffeine, ephedrine, and a combination of ephedrine plus caffeine on muscle endurance in men performing

weight circuit training. This trial showed an improvement in muscle endurance, but only on the first of three repetitions. The most recent trial[133] reported that, compared to placebo, ephedrine plus caffeine consistently improved exercise performance during stationary biking. The Bell trials are summarized in more detail in Table 18.

A trial by Sidney[134] assessed the effects of ephedrine versus placebo or no treatment (for baseline measures) on performance on a variety of physical function tests among 21 healthy young men. No statistical differences were seen among the groups on performance of any of the tests, including VO_2, measures of endurance and power, reaction time, hand-eye coordination, speed, and self-perceived exertion. These results agree with the finding by Bell and colleagues that ephedrine alone did not demonstrate significant effects on athletic performance.

In conclusion, the effects of ephedrine on athletic performance have not been well studied. The populations studied have been small and exclusively male, and the method of administration of ephedrine does not replicate the patterns of use reported for the general public. Effects of ephedrine on exercise performance are most often studied acutely (e.g., one to two hours after a single dose) in contrast to assessing the effects of chronic use on conditioning and performance. The one trial that did assess the effect on strength training did not find a sustained benefit of ephedrine supplementation. In addition, to show even a short-term effect of ephedrine, combination with caffeine was required. We identified no trials that assessed the sustained effect of ephedrine on aerobic conditioning or strength training and no trials that tested the effects of herbal ephedra on athletic performance.

Safety Assessment

Controlled Trials

We initially considered all 52 clinical trials of ephedra and ephedrine for the safety assessment. Two trials were excluded from the odds ratio meta-analysis because they did not contain a placebo group.[113, 138] Numerous symptoms were reported as adverse events. We grouped clinically similar symptoms as follows:

- Psychiatric symptoms: those symptoms described in the original clinical trials as "euphoria," "neurotic behavior," "agitation," "neuropsychiatric," "depressed mood," "giddiness," "irritability," and "anxiety;"

- Autonomic hyperactivity: those symptoms described in the original clinical trials as "tremor," "twitching," "jitteriness," "insomnia," "difficulty sleeping," "sweating," "increased sweating," and "increased perspiration;"

- Nausea/ vomiting: those symptoms described in the original clinical trials as "nausea," "vomiting," "abdominal pain," "upset stomach," "heartburn," and "gastroesophageal reflux;"

- Palpitations: those symptoms described in the original clinical trials as "palpitations," "irregular heartbeat," "loud heartbeat," "heart pounding," and "increased or stronger heartbeat;"

- Tachycardia: those symptoms described in the original clinical trials as "tachycardia" and "slightly elevated heart rate;"

- Hypertension: those symptoms described in the original clinical trials as "hypertension," "increased systolic blood pressure," and "increased diastolic blood pressure;" and

- Headache.

Table 19 presents the pooled estimate of the odds ratio for those adverse events for which data were sufficient to justify meta-analysis. The odds ratio will slightly overestimate the risk ratio for these events, as they occurred in 10 to 20 percent of subjects. This analysis reports a statistically significant increase of between 2.15 and 3.64 percent in the odds for the adverse events of psychiatric symptoms, autonomic hyperactivity, nausea/vomiting, and palpitations. There is a trend toward an increase of similar magnitude in the report of hypertension, but this increase was not statistically significant. There was also a non-statistically significant trend towards an increase in headaches. There were too few trials of ephedra or ephedrine alone to support analyses specific to these products; the subgroup analysis of adverse events involving ephedrine plus caffeine was similar to the main analysis. In our dose analysis, there was a trend toward higher risk of adverse events with higher doses of ephedrine, but data were sparse, and these differences were not statistically significant (for example, adjusted odds ratios of autonomic hyperactivity were 3.0 and 12.5 for medium- and high-dose ephedrine respectively, but the 95% confidence intervals overlapped; adjusted odds ratios for the three cardiovascular outcomes combined were 2.7 and 7.9 for medium- and high-dose ephedrine, a difference that was not statistically significant). The pattern of symptoms with statistically significant increases in occurrence is consistent with the pharmacology of ephedrine.

Table 20 presents frequency data concerning the other adverse events reported in the clinical trials. Meta-analysis was not performed on these data, primarily due to small numbers of events.

No serious adverse events (e.g., death, myocardial infarction, stroke, etc.) were reported in the 52 clinical trials that reported sample sizes. Therefore, the rate for these adverse events is zero. Even in aggregate, these trials had sufficient statistical power only to detect a serious adverse event rate of 1.0 in 1000, given the small numbers of patients studied in these trials. For trials of ephedra, statistical power in aggregate was sufficient only to detect a rate of serious adverse events of 4.0 in 1000. A conventional definition of a "rare" adverse event is about 1 in 1000. We also note that these data come from patients enrolled in clinical trials: Data from the pharmaceutical literature support the contention that patients taking pharmaceuticals outside of clinical trials may have a greater risk of particular adverse events than do patients selected to participate in clinical trials.[139] Therefore, in community practice, the rate for serious adverse events may be higher than that seen in clinical trials.

Case Reports

Because, even in aggregate, the numbers of subjects enrolled in clinical trials have been too small to assess the possibility of rare but serious side effects, we assessed case reports of serious events allegedly associated with ephedra use.

FDA Medwatch Data and Literature Cases

Figure 17 is a graphical representation of the case report evidence used in the safety assessment. The first master list produced by the FDA's Office of Nutritional Products, Labeling, and Dietary Supplements contained 1,848 adverse event reports. The second master list, from which events associated with ephedrine were removed, contained 1,783 reports. When we combined event reports of identical ID number but different products, we reduced the observations by 88 to 1,695 total observations but did not lose any data. In addition, we removed 137 reports listed in the master Excel file as having been filed after our September 30, 2001 cut-off date. The master Excel list also contained 214 reports (dated before September 30, 2001) for which no PDF data files existed on the CDs. Because documentation was essential for review of each report, these reports were removed from our analysis, which left 1,344 reports in our final dataset. In Table 21, we show the result of a chi-squared test of independence, which tests the association between the type of event distribution (death; stroke; myocardial infarction; other) and the type of data (available; after September 30, 2001; not available). This test rejected the null hypothesis of no association ($p < 0.001$), indicating that the distribution of events was different for the different data types. Thus, bias may exist, because the events we included were different in type than those we had to exclude. Since more cases of death were reported, as a percentage of total cases, in the data subsequent to September 2001, it is possible that our results would be different had we had the opportunity to include the cases filed after September 2001.

To the 1,344 unique and available reports that met the cut-off date (Batch 1), the FDA added another 125 reports (Batch 2) that consisted predominately of adverse events related to ephedrine. Together, 1,469 reports from the FDA MedWatch files were reviewed. Within the 1,344 reports from Batch 1, 158 cases reported on the most serious adverse events (death, stroke, and myocardial infarction), and 1,186 reported on other adverse events according to the master Excel spreadsheet. Of the 1,186 case reports, we found 944 reports that fit the categories of "other serious cardiovascular," other serious neurological," and "psychiatric." (We did not examine the remaining 242 adverse event reports because the descriptors in the master excel spreadsheet appeared to fall outside our focus of serious adverse events.) The 944 reports contained data on 975 subjects, of which 925 reported taking ephedra. From the brief review, we determined that 164 of these subjects reported events serious enough (ventricular tachycardia/fibrillation, cardiac arrest, pulmonary arrest, transient ischemic attack, brain hemorrhage, seizure, or psychiatric symptoms) to warrant including their file in the more detailed review. Within the 125 reports of Batch 2 (reporting on 130 subjects), we found 106 subjects reporting ephedra or ephedrine use. Thirty-three of those subjects reported events serious enough (ventricular tachycardia/fibrillation, cardiac arrest, pulmonary arrest, transient ischemic attack, brain hemorrhage, seizure, or psychiatric symptoms) to warrant including their file in the more detailed review.

Of the 530 articles retrieved from the medical literature for this report, 195 described adverse events. Of the 195, sixty-five were rejected from the adverse events analysis for the following reasons: 23 were descriptive; 20 were review articles; two were not controlled trials; 18 were RCTs or CCTs of ephedrine use in normal persons or patients with asthma or nasal congestion or its use in labor and delivery, measuring either acute mental or physical effects or pharmacokinetics; one was a study of pharmacokinetics and cardiovascular effects of ephedra in normal adults; and one was an RCT of intramuscular ephedrine during spinal anesthesia for caesarean section. Of the remaining 130 articles reporting adverse events, 59 articles reported on 52 RCTs or CCTs. These articles contributed to the adverse events analysis already discussed. Seventy-one were case report or case series articles reporting adverse events; however, six articles were found to be duplicates of articles already included in the analysis.

From all sources, 84 deaths, 26 myocardial infarctions, 56 cerebral vascular accidents (strokes or cerebral hemorrhage), 30 "other cardiac" events, eight "other neurological" events, 40 cases of seizure, and 91 cases of psychiatric events. We identified two deaths, three myocardial infarctions, nine cerebrovascular accidents, three seizures, and five psychiatric cases as sentinel events with prior ephedra consumption. Three deaths, two myocardial infarctions, two cerebrovascular accidents, one seizure, and three psychiatric cases were identified as sentinel events with prior ephedrine consumption. We identified an additional 43 cases as possible sentinel events with prior ephedra consumption and an additional seven cases as possible sentinel events with prior ephedrine consumption. About half of the sentinel events occurred in persons aged 30 years or younger. Classification as a sentinel event does not imply a proven cause and effect relationship.

What follows are short descriptions of the adverse event cases that we reviewed further for other potential causes for the adverse event. Table 22 presents data abstracted from each reviewed case. Tables 23 and 24 summarize the adverse events by gender, age, and type of event. Cases classified as something other than sentinel events include, where feasible, our reasons for so classifying them. Clinical detail regarding outcome is recorded to the extent it was available in the source material.

Deaths

Sentinel Events

FDA Cases—Ephedra

A 21-year-old male collapsed and died during a physical agility run at school after taking Hydroxycut and Ripped Fuel one time to increase energy. At autopsy, ephedrine and caffeine were found in the blood at concentrations of 0.02 mg/l and 0.31 mg/l, respectively. Although the autopsy report itself was not included in the FDA documents we received, a detailed description of the autopsy was found in the police notes that were included in the FDA file. According to these notes, the autopsy report stated that the coronary arteries were normal and that the diagnosis was acute arrhythmia due to ephedrine. (13914)

A 22-year-old female who weighed 183 pounds collapsed and died while standing in line to purchase ice cream. She had a history of asthma that was characterized as "well-controlled." She had congenital hydrocephalus with a shunt placed. She was taking Slacker II. Ephedrine was found in the blood. The autopsy report stated that the coronary arteries were free of

atherosclerosis. There was no myocarditis. The brain was normal, except for the presence of the shunt. There was no other cause of death. The death certificate listed "cardiac arrhythmia due to ephedrine-containing diet medication." (14390)

FDA Cases—Ephedrine

A 30-year-old female died suddenly. Her husband stated that she had been taking MiniTabs in order to lose weight. She was found unresponsive by her husband and was brought to the emergency department in full cardiac arrest. Blood toxicology screen showed an ephedrine level of 24 micrograms (μg) per milliliter (ml). Examination of the heart and brain did not reveal any evidence of cause of death. Final pathological diagnosis included "acute drug toxicity–ephedrine" with the opinion that "this autopsy illustrates an instance of death due to acute drug toxicity." (3275432)

A 33-year-old male was found dead. He had been taking an over-the-counter preparation named "Max Brand Two-Way ephedrine tablets." Autopsy did not reveal any obvious cause of death, particularly with respect to the brain and heart. However, the blood ephedrine level was 13.4 μg per ml. The final pathological diagnosis was drug intoxication, with the opinion that the person died as the result of "drug intoxication with ephedrine." (3289590)

Literature Case—Ephedrine

A 28-year-old male truck driver was, according to his family, taking up to 600 mg of ephedrine per day for six years. After having consumed 250 mg of ephedrine one day, he collapsed while baling hay. Autopsy did not reveal any pathologic process to account for his death. "Specifically, the coronary arteries, valves, and myocardium, including the conduction system, were normal." Only ephedrine and guaifenesin were identified on toxicology screens. The conclusion was that death "was most likely due to a cardiac arrhythmia triggered by the combination of an excessive use of ephedrine and strenuous labor on a hot day." (348)

Possible Sentinel Events

FDA Cases—Ephedra

A 36-year-old female began taking Nature's Nutrition-Formula One in August 1993. In December 1993, she was taken to the emergency department and found to have low potassium but signed out Against Medical Advice. In May 1994, she had severe stomach cramps and later that day was found unconscious by her daughter. She was taken to the hospital, where she died five days later without having recovered consciousness. According to her husband, she had no history of heart, thyroid, or blood pressure problems. The medical record documents a past history of bulimia and anorexia. There is a brief autopsy form consisting of a series of hand-written notes and check marks. Next to the word "cardiovascular" is a handwritten check mark, suggesting the heart had been examined and found normal, but no dictation describes the heart. There is an extensive description of the brain, which was normal. Elsewhere in the medical chart is a statement that the patient was thought to have had an acute myocardial infarction with adult respiratory distress syndrome and heart failure. Her creatine phosphokinase (CPK) isoenzymes and myoglobin (MB) fractions were both elevated. The emergency department record reported a toxicology screen positive for ephedrine, phentermine, and chlorpheniramine. A cardiology note and an echocardiogram reported severe global cardiac dysfunction and a left ventricular ejection fraction of 25 percent. We classified this case as no higher than a possible sentinel event because

there was no evidence available to us of an adequate examination of the heart. It is possible that this woman could have had acute myocarditis, which led to global cardiac dysfunction. (9508)

A 32-year-old male truck driver was found dead in his truck by the police. In the truck were found Nature's Nutrition-Formula One, Nature's Nutrition-Formula Three, a bottle of Tylenol with codeine, Vicks Formula 44, Nyquil, Ibuprofen, and Rexall cold tablets. The FDA files do not contain a copy of the actual autopsy report, but notes state that the autopsy report said the heart was enlarged, the coronary arteries were normal, and there was a slight case of pneumonia. The cause of death was listed as myocarditis, bronchiolitis, and pneumonia. Toxicology screen was negative for ephedrine but did show pseudoephedrine and doxylamine. We classified this case as a possible sentinel event because the myocarditis could have contributed to his death and the etiology of the myocarditis is unknown. (10276)

A 38-year-old male collapsed and died after jogging. Prior to jogging, he had had a cup of coffee and Ripped Fuel supplements. At autopsy, he was found to have triple vessel coronary artery disease and cardiomegaly. Because of this preexisting condition, we classified this as a possible sentinel event. (12485)

A 21-year-old male on his college wrestling team was trying to lose weight, perhaps as much as 17 pounds in a few days, to achieve a weight limit for an upcoming meet. He had been taking Thermogenics Plus for an unknown length of time. He began to feel weak while sitting in the sauna. He left the sauna, went to get a drink, and collapsed. On autopsy, the cause of death was listed as sudden cardiovascular collapse with rhabdomyolysis and dehydration. The heart exam revealed normal coronary arteries. We classified this as a possible sentinel event since the intense effort to lose weight likely led to dehydration, which then led to cardiac collapse. (12722)

A 15-year-old female collapsed and died while playing soccer. She had been taking Ripped Fuel for an unknown length of time. At autopsy, she was found to have a congenital abnormality: an anomalous origin of the left coronary artery from the pulmonary circulation (the Bland-White-Garland Syndrome). This condition is not usually associated with life beyond infancy, if left uncorrected. Due to this preexisting condition, the case was classified as a possible sentinel event. (12843)

A 26-year-old male had been taking Ripped Fuel for two weeks prior to his death. There is no autopsy report in the FDA files, but detailed notes state that the autopsy revealed he died of acute aortic dissection. According to the file, he had been having back pain two weeks prior to his fatal event and went to the emergency department complaining of severe chest pains. He was diagnosed with esophagitis and sent home. Four days later, he returned to the emergency room again with severe chest pains and was told the source of his pain was the chest wall. The next day, he was found dead by his girlfriend. According to his family history, several relatives had also had an aortic dissection, including a niece who had had an aortic dissection at age 18. The notes state, "This appears to have been some form of genetic connective tissue abnormality." There is also evidence of prior borderline hypertension. Toxicology screen for cocaine, ephedrine, and amphetamines was negative. Only caffeine and acetaminophen were found in the blood. This case was classified as a possible sentinel event, because it appears the patient was genetically predisposed to aortic dissection. (13906)

A 26-year-old female was found dead by her father. She had been taking a product called Diet Fuel for six months. The adverse event report stated, "Coroner felt this was a massive heart attack." Autopsy concluded she suffered from tachycardia, high blood pressure, and restriction of the coronary artery. The death certificate stated that death was due to "dissection of the left anterior coronary artery." Ephedrine and pseudoephedrine were found in the blood. This case was classified as a possible sentinel event. (14019)

A 35-year-old male, who had been taking Hydroxycut for seven days to increase energy, came home from work early because he was not feeling well, went to the bathroom, and was later found unresponsive. At autopsy, an 80 percent stenosis of the proximal left anterior descending coronary artery was found, along with "moderate" stenosis of the right and left circumflex coronary arteries. The cause of death was listed as atherosclerotic coronary vascular disease. Because of this preexisting condition, we classified this case as a possible sentinel event. (14638)

Literature Case—Ephedra

A 23-year-old man was found dead in his apartment by his sister. He had been using Ripped Fuel. Autopsy showed "no gross evidence of a pathologic process." Microscopic examination of the heart reported "multifocal and confluent myocyte necrosis with healing of approximately 1 to 2 weeks; mild perivascular, focal endocardial, and focal epicardial fibrosis; and moderate myocyte hypertrophy and vascular congestion. There was no evidence of myocarditis." Blood toxicology screen was negative, but urine toxicology screen showed ephedrine at 1.6 μg per ml. We classified this case as a possible sentinel event. (258)

Literature Cases—Ephedrine

A 42-year-old male was found dead at home. On autopsy, he was found to have had an intracranial hemorrhage and was also found to have hypertensive cerebral vasculopathy. He had been taking a street drug ("speed") that contained ephedrine, and toxicology screen was positive for ephedrine at 2.7 μg per ml. We classified this case as a possible sentinel event due to the preexisting vasculopathy. (44)

An 84-year-old female was found in a coma and subsequently died. On clinical investigation, she was found on computerized tomography (CT) scan to have a subarachnoid hemorrhage and a right subdural hemorrhage. At autopsy, she was found to have a ruptured berry aneurysm along with cerebral atherosclerosis. She had been taking an unknown drug containing ephedrine, and her blood toxicology screen was positive for ephedrine. We classified this case as a possible sentinel event due to the preexisting berry aneurysm. (44)

A 44-year-old male was taking ephedrine as a replacement for daily coffee and cocoa. He had a sudden cardiorespiratory arrest and died. Autopsy revealed an acute thrombus in the left anterior descending coronary artery. The report states, "All other coronary lumina were patent, although calcified with focal narrowing to approximately 50 percent." Due to the preexisting coronary artery disease, we classified this case as a possible sentinel event. (224)

Probably Not Related

FDA Case—Ephedra

A 24-year-old male collapsed and died during a training run. He had reportedly taken Ripped Fuel, although none was found in his personal possessions, nor were traces of amphetamines found on toxicology screen (which looked for ephedrine as well). At autopsy, he was found to have died of massive sickle-cell crisis. As a result, we classified this case to be probably not related to ephedra use. (13672)

FDA Cases—Ephedrine

A 40-year-old male was taking Max Alert to stay awake on the job. He had "odd symptoms that were not a recognizable illness," described as "nausea, dizziness, sweats, irritability, dehydration, respiratory problems, etc." The report then states that he was killed in a car accident while driving. We classified this case as probably not related to ephedrine use and note that it may be the same case as Case 1902493, which has a virtually identical description, both cases having been filed within one month of each other. (1859087)

A young male was killed in an automobile accident while driving home in the early morning from his night shift job at a hotel. The patient had been using Max Alert to stay awake. The cause of death at autopsy was laceration of the aorta. We classified this case as probably not related. (1902493)

A 30-year-old male was found dead. He had had chronic low back pain and a chronic pain disorder and was on numerous medications. Autopsy did not reveal any cause of death; however, the toxicology screen was positive for alcohol, fentanyl, phenylpropanolamine, ephedrine, pseudoephedrine, bupropion, nordiazepam, alprazolam, chlordiazepoxide, and nortriptyline. Cause of death was listed as mixed drug and alcohol intoxication. We classified this case as probably not related. (3491515)

A 29-year-old male died. Toxicology screens of blood and urine revealed that he was positive for morphine, hydrocodone, acetaminophen, diphenhydramine, hydromophone, promethazine, dihydrocodeine, codeine, pseudoephedrine, ephedrine, brompheniramine, phenothiazine, cannabinoids, and nicotine. We judged this case as probably not related. (3772362)

Insufficient Information

FDA Cases—Ephedra

A 37-year-old male collapsed and died after taking Metabolife for weight loss and energy. At autopsy, ephedrine was found in the blood. In addition, one coronary artery was found to be 70 to 80 percent stenosed. These data were recorded on a single page of telephone conversation notes in the file. Because there was no other documentary evidence regarding this case, we classified it as having insufficient information to judge. (13806)

A 56-year-old male who had recently started taking Thermogen Plus Liquid fat complexor tablets was found slumped over in his bathtub after a barbecue. He had a history of hypertension and was on a calcium channel blocker as well as daily baby aspirin. Within the year prior to his death, he had had a normal treadmill test. He also had elevated cholesterol for at least four years

prior to his death. Four days before his death he was noted to have heartburn. No autopsy report was in the FDA records. A report of a phone conversation stated that the death certificate listed "cardiac arrhythmia of unknown etiology" as the cause of death. We counted this case as having insufficient information, because no autopsy report was available to us, and he had preexisting hypertension and elevated cholesterol. Without the finding of the autopsy report that detailed the examination of the cardiovascular system, we can come to no other conclusion. (14465)

Myocardial Infarctions/ Acute Coronary Syndromes

Sentinel Events

FDA Case—Ephedra

A 45-year-old male took two tablets of Nature's Nutrition-Formula One prior to suffering a myocardial infarction. The patient had also smoked for 30 years and had been a practicing alcoholic until one year prior to the event. At angiography, the coronary arteries were found to be normal. (10024)

FDA Case—Ephedrine

A 23-year-old female took four Midnight Ecstasy tablets as a sexual stimulant. Shortly thereafter, she began developing symptoms of autonomic hyperactivity followed by palpitations, shortness of breath, and pink frothy sputum. She was taken to the emergency room, where she was found to be in pulmonary edema. Cardiac enzymes indicated acute myocardial injury. Urine toxicology screen was positive for marijuana and amphetamines. Ephedrine was not mentioned in the toxicology report. Coronary angiography did not reveal any sign of coronary artery disease. Her recovery was complicated by a presumed infection, but she was ultimately discharged from the hospital in good condition. (3446357)

Literature Cases—Ephedra

A 30-year-old male body builder was taking ma huang "as instructed by the product label." He presented to the emergency department complaining of chest pain. Vital signs revealed tachycardia and no hypertension. Electrocardiogram was consistent with acute inferior cardiac ischemia. Cardiac enzymes confirmed a myocardial infarction. Urine toxicology screen was negative for cocaine and amphetamines. Emergency cardiac catheterization demonstrated normal coronary arteries with mild global left ventricular hypokinesis and mild left ventricle hypertrophy. He recovered well. (244)

A 19-year-old male experienced chests pains 30 minutes after taking Dymetadrine Xtreme at the recommended dose. Vital signs revealed tachycardia and elevated respiratory rate of 22. The physical examination was described as unremarkable except for diaphoresis. Electrocardiogram was consistent with an inferolateral myocardial infarction, and myocardial necrosis was confirmed by cardiac enzymes. Toxicology test was negative for cocaine. Cardiac catheterization was reported as showing "only minimal intimal disease of the distal left anterior descending artery." The patient was reported to have recovered well. (516)

Literature Case—Ephedrine

A 35-year old woman was taking a dietary supplement containing ephedrine for weight loss. She had the acute onset of chest pain, diaphoresis (perspiration), and shortness of breath. She was admitted to the hospital, where an electrocardiogram and cardiac enzymes were consistent

with acute myocardial infarction. Results of a cardiac catheterization were reported as "normal cardiac function and normal coronary arteries." She was discharged with a diagnosis of acute myocardial infarction secondary to cardiac spasm. (224)

Possible Sentinel Events

FDA Cases—Ephedra

A 37-year-old male took E'ola Amp II Pro Drops for twelve days prior to suffering an inferior myocardial infarction. At coronary angiography, his mid-right coronary artery was found to be 95 percent stenosed. The patient received percutaneous transluminal coronary angioplasty. Due to the preexisting condition, we classified this case as a possible sentinel event and note the product was later reported to include illegal doses of ephedrine. (9372)

A 54-year old-male with a history of hypertension had been taking Nature's Nutrition-Formula One for approximately three to four months prior to suffering an inferior myocardial infarction. He also had a cardiac arrest from which he was successfully resuscitated. On angiography, he was found to have an 80 percent stenosis of the right coronary artery along with total occlusion of the obtuse marginal artery. He was treated with angioplasty. Because of the preexisting condition, we classified this case as a possible sentinel event. (9504)

A 35-year-old male took five capsules of Metabolift prior to a vigorous workout. He then had an acute inferior myocardial infarction, for which he received thrombolytic therapy. At angiography, his left anterior descending coronary artery had ectasia, which is indicative of coronary artery disease. Therefore, we classified this case as a possible sentinel event. (10009)

A 38-year-old female took Herbalife Original Green for one day. The next day, she suffered an inferior myocardial infarction, for which she received thrombolytic therapy. At catheterization, the posterior descending artery was found to be totally obstructed. The left coronary artery was found to be normal except for one area with a 70 percent lesion. The toxicology screen was negative for cocaine but positive for amphetamines. Ephedrine was not mentioned in the toxicology report. The diagnosis was "presumed right coronary spasm with Prinzmetal's Angina." In the setting of coronary artery disease, we classified this case as a possible sentinel event. (13009)

A 37-year-old female with a family history of coronary artery disease was both overweight and a cigarette smoker. She was taking Metabolife 356 to lose weight. She suffered a myocardial infarction and was found on angiography to have total occlusion of the right coronary artery with diffuse disease in the left anterior descending coronary artery and the left circumflex artery. She received percutaneous transluminal coronary angioplasty with placement of a stent. Because of the preexisting condition, we classified this case as a possible sentinel event. (14114)

A 43-year-old female had a heart attack. Earlier that day, she had taken six tablets of Metab-O-Lite. She was a cigarette smoker and had a lipid disorder. At coronary catheterization, the left main coronary artery was found to be normal, the left anterior descending artery had 20–30 percent stenosis, the left circumflex artery had no disease, and the right coronary artery had 30 percent stenosis. Because of the preexisting coronary artery disease, we classified this case as a possible sentinel event. (14530)

Cerebrovascular Accident/Stroke

Sentinel Events

FDA Cases—Ephedra

A 26-year-old female began taking Thermo Slim and The Accelerator daily for weight loss. Three days later, her legs became weak, and she reported feeling like she was going to pass out. She was taken to the emergency room where she was found to have a probable basal ganglia hemorrhage on CT scan. She also had paranoid psychosis. She was a long-time intravenous drug abuser and alcohol abuser. She had also smoked cigarettes for ten years. She was not taking oral contraceptive pills. Blood pressure in the emergency room was 129/71. Toxicology screen was positive for acetone and for benzodiazapines. It was negative for cocaine, amphetamines, and a host of other substances, but ephedrine was not specifically examined. Ephedrine was not mentioned in the toxicology report. She signed out Against Medical Advice from that hospital and ended up in another hospital later that day in restraints. Another toxicology screen was positive for phenylpropanolamine and benzodiazepine. At this hospital, rheumatologic and embolic evaluation was negative. (10874)

A 42-year-old female who was taking Power Trim began having headaches. Approximately one week later, when she was scheduled to undergo a root canal procedure to treat a dental abscess, her daughter heard a "thump" on the floor and found her mother shaking, lying on the floor, unresponsive. She was taken by ambulance to the emergency room, where she was observed to have a focal seizure, which then generalized. She had no prior history of seizure. Toxicology screen was negative. Glucose was 93. CT scan revealed a possible small area of hemorrhage in the upper right parietal region. An MRI with contrast revealed a 1 by 1-1/2 centimeter area of acute hemorrhage without mass effect and without abnormal vascularity. Digital subtraction angiography did not reveal any evidence of arteriovenous malformation. The patient remained seizure-free on anticonvulsant therapy. (11062)

A 31-year-old female had been taking Trim Easy for weight loss for nine months. She occasionally took up to 6 caplets at a time and smoked 3–4 cigarettes a day. She was found in the bathroom unconscious and brought to an emergency room. Her blood pressure was 143/86. CT scan showed a large intracerebral hematoma. Cerebral angiography did not show any source of the hemorrhage, and MRI also was remarkable only for the bleed. Medical records documented improvement over a period of time, but she was left with substantial physical limitations. (11105)

A 28-year-old male who was described as a weight trainer took Ripped Fuel. He also smoked two packs of cigarettes per day. During sexual relations with his wife, he had a headache and became dizzy. He was taken to the emergency department where he was found to have a right middle cerebral artery infarction that was "suggestive of vasospastic phenomenon." At the time of his admission, his blood pressure was 132/78. His toxicological examination was positive for benzodiazapines. Ephedrine was not mentioned in the toxicology report. Cerebral angiogram was negative. Rheumatologic and hypercoagulability evaluations were negative. There was a negative transesophageal echocardiogram. Urine screen showed ephedrine, pseudoephedrine, and caffeine, according to a discharge summary, which also described the illness as "cerebral infarction associated with ephedrine and caffeine use." (11675)

A 39-year-old male Navy diver, who regularly took Ultimate Orange for energy, presented to the ship doctor with right hand and leg numbness. The symptoms had occurred 1½ hours after using the product, during a workout. He also reported taking omeprazole, creatine, and vitamins. CT scan and angiogram were negative except for an intracerebral hemorrhage. Blood pressure initially was 140/72. The patient made a good recovery and was able to go back to work but was prohibited from further diving. (12980)

A 29-year-old male in the Army, who was taking Ultimate Orange and had a history of migraine headaches, reported that he was running on a treadmill, when he experienced "the worst headache of his life." He was taken to the emergency department, where he had some right-sided weakness, which improved over the next 12 hours. The CT scan and lumbar puncture were normal. The following morning, most of his symptoms had resolved, but then he suddenly developed total hemiplegia. He underwent an emergency MRI and angiogram, which showed a complete occlusion of the right middle cerebral artery. The patient had a very stormy course, ultimately resulting in a right hemispherectomy to control swelling. A full hypercoagulability workup was done and was normal. Echocardiogram did not reveal an embolic source. Microscopic examination of the brain tissue did not show any sign of vasculitis. (13418)

A 53-year-old female was taking Slim Caps. In June 2000, she presented with the clumsy hand syndrome on the right. At the time, her blood pressure was 204/128. She stated that in the past, her systolic blood pressure had been 135. CT scan at the time of the event showed a lacunar infarct in the right frontal parietal region. She made a good recovery. A hypercoagulability workup was negative. Echocardiogram was done and showed no evidence of clot. (14372)

A 46-year-old female took Xenadrine for 4 days. While at work, she stood up, had a seizure, and became unresponsive. She was taken to the emergency department. A CT scan showed a left-sided frontal cortex stroke. MRI showed occlusion of the left middle cerebral artery. Blood pressure in the emergency room was 102/69. MR angiography was negative. Transesophageal echocardiogram was negative. Hypercoagulability workup was negative. (14473)

Literature Case—Ephedra

A 33-year-old male presented to the emergency department with the sudden onset of left hemiparesis and slurred speech. He smoked one pack of cigarettes a day and took bupropion for smoking cessation. He consumed Thermadrene 8 hours prior to the onset of neurologic symptoms. There was no hypertension. A noncontrast CT scan did not show any abnormalities. There was no evidence of intracerebral hemorrhage. He was treated with tissue plasminogen activator. Normal tests included a sedimentation rate, clotting studies, urine toxicology screen, homocysteine, antinuclear antibodies, Factor V level, complete hypercoagulability evaluation, echocardiogram, VDRL, and carotid and vertebral duplex studies. He was given a diagnosis of new cerebrovascular accident in the right middle cerebral artery. He was left with a permanent disability. (552)

Literature Cases—Ephedrine

A 19-year-old female with a history of anorexia/bulimia and alcoholism presented after taking 15 to 18 tablets that contained ephedrine 25 mg (along with guaifenesin). She had previously been taking this product 3 to 10 tablets at a time to lose weight, and the case report

was silent regarding whether or not this increased dose was a suicide attempt. Initial presentation was unremarkable, but while in the emergency department, she developed a severe headache and right-sided paralysis. Blood pressure was elevated at 136/98. A CT scan showed left parieto-frontal cerebral hemorrhage with extension into the left lateral ventricle. Angiography did not document a source of the bleed. She was treated with an emergency craniotomy and hematoma evacuation. No arteriovenous malformation was found. She survived but had a major residual neurologic deficit. We classified this case as a sentinel event, but also note this may have been an unrecognized suicide attempt. (184)

A 20-year-old woman took two capsules of a "purported amphetamine look-alike." Two hours after consumption, she developed a severe headache, nausea, hemiparesis, and aphasia. Ten hours later, she sought admission to a hospital. On initial evaluation, her blood pressure was not elevated and she had a right homonymous hemianopsia and a dense right spastic hemiparesis. At that time, sedimentation rate, clotting studies, rheumatologic studies, and other tests evaluating both vasculitis and the hypercoagulable state were negative. CT scan showed a left external capsular hemorrhage with shift of the midline structures. Angiography showed alternating narrowing and dilation of several branches of the middle cerebral artery. She made a slow and incomplete recovery. Analysis of the capsules demonstrated the presence of ephedrine, phenylpropanolamine, and caffeine. (514)

Possible Sentinel Events

FDA Cases—Ephedra

A 32-year-old female who was taking E'ola Amp II Pro Drops for weight loss suffered a brain stem stroke. She had been to the emergency room twice earlier in the day prior to her stroke and both times was thought to be having an allergic reaction to peanut butter. She was taking oral contraceptive pills. Evaluation of the cause of her stroke included a transesophageal echocardiogram that was negative except for an atrial septal aneurysm, but this was not thought to be the cause of the stroke. Lumbar puncture was negative. Cerebral angiography showed the basal artery was occluded with embolus. Because no hypercoagulability workup was noted, we could not judge this case as more than a possible sentinel event, and also note this product was later reported to include illegal doses of ephedrine. (9296)

A 56-year-old female who was taking E'ola Amp II Pro Drops for three months suffered a lacunar infarct. She had preexisting hypertension, total cholesterol of 238, and triglycerides of 529. She also had a 60-pack-per-year history of smoking. CT scan was negative. The MRI revealed microvascular changes. Because of her preexisting conditions, we classified this case as a possible sentinel event, and also note this product was later reported to include illegal doses of ephedrine. (9335)

A 24-year-old female had a right internal capsule stroke after taking one dose of Super Fat Burners. She was not taking oral contraceptive pills or on any other medications. Carotid arteriogram was normal, echocardiogram was normal, and drug screen was negative. She had had two miscarriages in the past. While most of the hypercoagulability evaluation was normal, one test suggested the presence of the lupus anticoagulant. Because the antiphospholipid antibody syndrome was not effectively excluded, we classified this case as a possible sentinel event. (10094)

A 64-year-old female with a history of hypertension, paroxysmal atrial fibrillation, and two transient ischemic attacks was on propranolol, isradipine, and aspirin therapy, and had taken Fit America Natural Weight Control Aid. She was found unconscious in the bathroom by her husband and taken to the emergency room, where she was found to have had an embolic stroke. She was given heparin, which resulted in a small left temporal parietal intracerebral hemorrhage. She was found to be in atrial fibrillation. Carotid ultrasound was negative. Due to the preexisting condition of atrial fibrillation, we classified this case as a possible sentinel event. (12713)

A 47-year-old male, who had a long history of hypertension but had not taken medication in 20 years, suffered a right lentiform nucleus bleed that manifested itself as left-sided paralysis. The notes stated that just prior to the event, he took Purple Blast to lose weight; however, there was no drug or alcohol use. When he arrived in the emergency department, his blood pressure was 196/94, and it later fell to 187/107. Chest x-ray revealed cardiomegaly. CT scan showed "large acute intracranial hemorrhage in mid portion of right cerebral hemisphere." His triglyceride levels were 364. Because of the history of long-standing untreated hypertension, we classified this case as a possible sentinel event. (12733)

A 41-year-old female with a history of hypertension who had been taking Diet Phen and had four stroke events over a two-month period. Blood pressure in the emergency department after one event was 170/108, and at another time, it was 158/99. She was put on coumadin and discharged home after her first stroke but then was readmitted three times in the next two months for recurrent stroke, all of which occurred while she was on anticoagulants. She suffered additional neurologic events consistent with brain stem infarction. She had numerous magnetic resonance angiograms, the first of which revealed an "irregularity of the basilar artery." Subsequent studies showed the basilar artery totally occluded. The interpretation of these angiograms was the subject of considerable discussion, with the final interpretation in the notes being "basilar artery vasculitis." Rheumatologic evaluation and hypercoagulability evaluation were negative. This case was difficult for us to assess since amphetamines have been linked to vasculitis, but her vasculitis could also have had other etiologies and therefore we classified this case as a possible sentinel event. (12888)

A 25-year-old female who was taking Natural Trim presented with slurred speech and right-sided weakness. She was not on oral contraceptives and was a nonsmoker for five months. Blood pressure recorded in the nurse's notes was 144/88. MRI revealed a lacunar stroke. Carotid duplex was negative. Echocardiogram showed a mitral valve prolapse with a patent foramen ovale with a right-to-left shunt that was described as minimal. No clot was seen. The patient had total resolution of symptoms. Hypercoagulable workup was normal, but incomplete. No tests of protein S or C (proteins involved in blood clotting) were reported in the FDA material. Therefore, we classified this case as a possible sentinel event. (14378)

A 42-year-old male who was taking Slim 'N Up awoke with paresthesia on the left and difficulty walking and talking. He was a nonsmoker for five years. The patient had a known diagnosis of hypertension, was on Diltiazem, and also had hypercholesterolemia. Emergency department blood pressure was 132/89. Lumbar puncture in the emergency room was traumatic, with 35 red blood cells in tube 1 and 0 red blood cells in tube 4. A transcranial Doppler study was negative, carotid duplex study was negative, echocardiogram was negative, and MRI

showed left cerebella infarct. Subsequent admissions were for seizure control. We classified this case as a possible sentinel event due to the prior hypertension and hypercholesterolemia and the lack of complete hypercoagulability workup. (14434)

A 55-year-old female who had been taking Metabolife 356 for 60 days developed a headache, had a seizure, and became unconscious. She was taken to the emergency department, where she was found to have a large subarachnoid hemorrhage. An emergency angiogram showed a large right posterior communicating artery aneurysm, which was subsequently clipped. She had a stormy course complicated by meningitis, hydrocephalus, and placement of a ventricular peritoneal shunt. Because of the preexisting large aneurysm, we classified this case as a possible sentinel event. (14553)

Literature Case—Ephedra

A 33-year-old man who had been taking ma huang (40–60 mg per day of ephedra alkaloids) for energy and weight training awoke with a severe Wernicke's aphasia. He had not complained of prior headache or other symptoms. He had a slight right-sided facial and arm weakness and a right Babinski sign. His blood pressure was 140/60, and his pulse was 54 per minute. Brain CT showed signs of extensive left middle cerebral artery infarct. Cervical ultrasound duplex scanning and cerebral angiography were normal. Cerebral CSF examination was normal. The report contained no coagulopathy assessment other than D-dimers (cross-linked fibrin molecules that may be a diagnostic marker for venous thromboembolism), which were within the normal range. Creatinine was in the normal range. Transesophageal echocardiography and ECG were also normal except for a patent foramen ovale. We classified this case as a possible sentinel event, because there was no additional documentation about the details of the coagulopathy evaluation. (270)

Literature Cases—Ephedrine

A 37-year-old male who ingested 10 pills of a "street drug" containing ephedrine (15.3 mg per tablet, as identified by subsequent analysis), developed sudden right body numbness and, on evaluation, was found to have pure right body sensory loss with a left thalamic infarct on MRI. Laboratory studies included normal prothrombin time and partial thromboplastin times, sedimentation rate, electrocardiogram and transthoracic electrocardiogram. The patient refused arteriography. As a result, we classified this case as a possible sentinel event. (44)

A 20-year-old man was admitted with nausea, vomiting, and headache that began one hour after he took an unknown quantity of what he called "speed." Urine drug screen on the day of admission revealed only ephedrine, in particular excluding amphetamine, phenylpropanolamine, caffeine, and other drugs. CT scan obtained on admission demonstrated blood in the subarachnoid space, which was confirmed by lumbar puncture. Angiography on the day of admission was normal, and rheumatologic evaluation was negative. A repeat angiogram seven days later showed features typical of vasculitis. We classified this case as a possible sentinel event. (438)

Insufficient Information

FDA Cases—Ephedra

A 36-year-old female who was taking Nature's Nutrition-Formula One for weight loss developed a headache. Based on CT and MRI, she was diagnosed as having had a stroke. She was a nonsmoker and was not taking oral contraceptive pills. This information was obtained from notes of a conversation with the patient herself. The notes stated that medical records were requested; however, none appeared in the FDA file. Therefore, we classified this case as having insufficient information. (9521)

A 30-year-old female who took Metabolife 356 for one week developed a headache while eating and had a stroke. A friend drove her to the hospital; en route, they encountered a paramedic, who obtained a blood pressure reading of 249/131. She stated that she was on no medications, had no hypertension, didn't smoke, and didn't drink. Unfortunately, no additional information appeared in this record. Therefore, we classified this case as having insufficient information. (13829)

A 36-year-old female who took Metabolife 356 had "respiratory failure and a possible stroke." The file contains a note stating that medical records were requested but were never received. Thus, we classified this case as having insufficient information. (13905)

FDA Case—Ephedrine

A 32-year-old female who, according to case notes, was taking over 100 "Maxi Thins" per day for five years and was "addicted to product," had three cerebral hemorrhages and two strokes and was hospitalized for two months. No additional information is available. Thus, we classified this case as having insufficient information and also note the extraordinary dose of ephedrine being consumed. (1823550)

Literature Case—Ephedrine

A 68-year-old man who had been taking an "over-the-counter anti-asthma pill" containing 40–60 mg of ephedrine per day for 10 years had a left temporal-parietal hematoma with rupture into the lateral ventricle. Angiography showed changes consistent with vasculitis, and pathological examination from material obtained during surgical evacuation of his hematoma showed necrotizing angiitis of the small vessels. The patient improved with prednisone. We classified this case as having insufficient information. (515)

Other Cardiac and Other Neurological Cases

Near Sudden Death

A 22-year-old male who regularly used Ripped Force along with a variety of other supplements collapsed while lifting weights and had a ventricular fibrillation cardiac arrest complicated by hypoxic encephalopathy. Although he had a history of asthma, this was not felt to be an asthmatic attack. Toxicological examination revealed ephedrine, pseudoephedrine, methyl ephedrine, and phenylpropanolamine. An echocardiogram ruled out asymmetric septal hypertrophy but did reveal a reduced left ventricular ejection fraction (35–40 percent) and an increased left ventricular end diastolic dimension. CT scan showed no brain tumor or bleed. A pulmonary consultant who saw him in the hospital stated that he "doubts" that this incident was related to asthma. He recovered to the point where he could feed himself but he does not

remember his friends and has substantial mental disability. We classified this as a possible sentinel event since the echocardiogram results raise the possibility that this patient could have had a cardiomyopathy, which then could be the cause of the cardiac arrest. (12851)

A 28-year-old female who took Herbalife Original Green had a cardiac arrest later that same day while playing softball. According to the affidavit, she needed to be defibrillated four times and now has a permanently implanted defibrillator. Unfortunately, other than this affidavit, no information was available. Therefore, we classified this case as having insufficient information. (13031)

A 32-year-old female had been taking Natural Trim for two weeks. On one morning, after taking Natural Trim, she ate lunch, went outside her office building to smoke a cigarette, and had a witnessed cardiac arrest. A physician bystander initiated CPR, and she was taken to the Emergency Department with decorticate posturing. Although successfully resuscitated, she was left with permanent heart and brain damage. She also had a permanent intracardiac defibrillator implanted. Notes from the FDA investigator said that her hospital records showed she had chronic obstructive pulmonary disease, ventricular fibrillation, and "cardiomyopathy versus acute myocarditis" with "possible contributing factor of cardiotoxic diet pill." She had a left ventricular ejection fraction of 35 percent with global left ventricular hypokinesia, and endomyocardial biopsy found mild focal hypertrophy and mild focal interstitial fibrosis. No medical records were available in the FDA files. Therefore, we classified this case as having insufficient information. (13643)

Cardiomyopathy

A 28-year-old female who had been taking ephedrine tablets (2000 mg per day) for eight years to lose weight presented with dilated cardiomyopathy. She denied any other chronic alcohol or drug use except tobacco. She reported that after abruptly reducing the dose of ephedrine to only 75 mg per day, she rapidly developed symptoms of dyspnea, fatigue, and orthopnea (difficulty breathing while lying flat). Exhaustive diagnostic evaluation, including cardiac catheterization and endomyocardial biopsy, revealed no specific diagnosis, and the patient's dilated cardiomyopathy was characterized as idiopathic. We classified this case as a possible sentinel event, but note the extraordinary level of ephedrine use. (110)

A 39-year-old male with a history of hypertension presented with dyspnea on exertion, orthopnea, and edema. He had been taking numerous Herbalife supplements (including Original Green) for three months, which provided a total of between 7 and 21 mg of ephedrine alkaloid daily. Exhaustive diagnostic evaluation, including endomyocardial biopsy, yielded a diagnosis of hypersensitivity or eosinophilic myocarditis. He was treated with azothioprine and prednisone, and Herbalife medications were discontinued. At six months follow-up, his heart function was normal. We classified this as a possible sentinel event. (297)

A 32-year-old housewife who was noted to be abusing ephedrine, taking up to 450 mg a day, presented with "congestive cardiac failure" and received a clinical diagnosis of congestive cardiomyopathy of unknown etiology. No coronary angiography or myocardial biopsy was performed, which may have been within the standard of practice at the time of the case (1980).

We classified this case as having insufficient information and also note the high level of ephedrine intake. (260)

A 65-year-old female who had been taking the product Thermolean for two years was hospitalized with acute congestive heart failure. Evaluation revealed cardiomyopathy with a left ventricular ejection fraction estimated at 15 percent and atrial fibrillation. It was the treating physician's opinion that the cardiomyopathy was "probably secondary to ephedrine use." There were no medical records available with this file. Therefore, we classified this case as having insufficient information. (13793)

Ventricular Tachycardia

A 48-year-old female was taking Metabolife 356 for approximately one month when she developed a rapid heartbeat that would not subside. She was taken to the emergency department and found to be in ventricular tachycardia. The file contained no information on diagnosis or treatment procedures, although the MedWatch form stated that the patient said she was taking beta-blockers. No medical records were available for this adverse event. Therefore, we classified this case as having insufficient information. (13945)

Transient Ischemic Attack

A 57-year-old female with prior history of hypothyroidism, gastroesophageal reflux disease, depression, degenerative joint disease, and fibromyalgia began having nausea and vomiting and became disoriented. She had been taking Synthroid, Oxycontin, Prozac, Trazodone, Prilosec, and one other medication whose name was illegible in the file notes. She also took Metabolife 356 for one day and a total of 48 mg of ephedrine prior to the adverse events. Her husband took her to the emergency department, where an examination was inconclusive. Laboratory values were essentially normal. A toxicology screen was positive for opiates but negative for amphetamines. A CT scan was negative. She was seen in consultation by a neurologist who told her that she had a vasospasm transient ischemic attack, possibly related to ephedrine use, and the discharge instructions were to stop using the Metabolife 356 supplement. We classified this case as a possible sentinel event, because the symptoms alone do not confirm that she had a transient ischemic attack. (13062)

Seizure

Sentinel Events

FDA Case—Ephedra

A 19-year-old female who reported using Shape Rite/Shape Fast at half the recommended dose for three to four weeks had one witnessed episode in which her "arms and legs went stiff, noticeable drool appeared, eyes rolled, [and she] appeared to black out," followed by a postictal period (period of confusion typically observed following a seizure). She had no prior history of seizures. Electrolytes were normal; complete blood work was normal; and pregnancy test was negative. She had a normal CT scan without contrast and a normal electroencephalogram. She was seen by a consultant neurologist, whose diagnosis was that she had a "single-tonic seizure, and none of the other factors which (*sic*) are normally associated with seizures, are present." (10974)

Literature Case—Ephedrine

A 38-year-old female with no prior seizure history experienced two "petit mal" seizures (the authors' description) after taking two tablets of over-the-counter ephedrine-containing dietary supplements in the morning and evening. The following day, she had a generalized tonic-clonic seizure, during which she required respiratory assistance. Over the next five days, she continued to have petit mal and generalized tonic-clonic seizures. She was diagnosed with new onset of tonic-clonic seizures with complex partial seizures. The report (in *Morbidity and Mortality Weekly*) stated, "Other possible causes of seizures were excluded." After discontinuing the ephedrine-containing dietary supplement, she had no further seizures. (224)

Possible Sentinel Events

FDA Cases—Ephedra

A 47-year-old female who had been taking Nature's Nutrition-Formula One for three weeks to lose weight (one pill twice a day) had a tonic-clonic seizure in her sleep at 2 a.m. Her husband took her to the emergency department, where some evaluation was done, but she was treated and released on no therapy. Two months later, she had another seizure, which occurred at 5 a.m. At that time, she was transported by ambulance to the emergency department and was seen by a neurologist. A random glucose was 90, electrolytes were normal, sedimentation rate was 52, MRI was normal, and EEG was described as "mildly abnormal." She had a remote history of hysterectomy and ear surgery two years prior to the event. Her only medication was Premarin, and she used alcohol only socially. It was the neurologist's opinion that the patient had new onset generalized tonic-clonic seizures, and "hypoglycemia" was suspected but could not be proved. The patient's subsequent course was complicated by rash, fever, mild pancytopenia, and increased liver function tests, which were thought due to her anticonvulsive therapy. We classified this case as a possible sentinel event, because other causes were considered and not effectively excluded. (9534)

A 37-year-old female who was taking Nature's Nutrition-Formula One was admitted to the hospital for symptoms of dizziness, shortness of breath, palpitations, and "passing out," and "intermittent episodes of confusion," with one episode of "shaking of limbs and saliva coming out of her mouth." She had no prior history of seizures. She denied using alcohol. She was seen in consultation by a neurologist. Electrolytes were normal, complete blood count was normal, arterial blood gas was normal, glucose was 179, magnesium was normal, toxicology screen was negative, pregnancy test was negative, CT scan with and without contrast was read as a "0.8 by 0.6 centimeter calcification in the frontal region, which may represent dural calcification." Subsequent MRI was normal and showed no evidence of calcification in the area seen on CT scan. Mild chronic right sinusitis was noted. EEG was interpreted as mildly abnormal due to "excessive intermittent bi-temporal slowing." No epileptogenic activity was seen. The impression of the neurologist was "complex seizures with generalization." We classified this case as a possible sentinel event. (10221)

A 62-year-old male who had been taking the product Thermo Slim for three to four months for weight loss began to have periods of memory loss, confusion, and agitation. He then had a generalized seizure with lateralizing features characterized by right sided tonic-clonic jerking and was admitted to the hospital. The patient had a prior history of heavy alcohol consumption until approximately four years before the event. In the emergency room, the patient was noted to

be normotensive and had no fever. He was characterized to be in acute delirium. Although he had no prior history of diabetes mellitus, his blood sugar on admission was 488, and he was given the diagnosis of diabetes. Toxicology screen was positive for benzodiazepines. Arterial blood gases revealed adequate oxygenation. CT scan of the brain without contrast showed atrophy but was otherwise unremarkable. MRI showed generalized brain atrophy. Electroencephalogram showed "moderate to severe abnormality, with bilateral cerebral dysfunction;" however, no epileptiform activity was identified. He was given a diagnosis of organic brain syndrome with senile dementia and also the possibility of "left temporal lobe cerebral infarct with secondary seizure." One consultant raised the possibility of acute encephalopathy of uncertain etiology. Because of the focal nature of the seizures and the multiple metabolic problems, we classified this case as a possible sentinel event. (10432)

A 23-year-old female was taking Metabolife 356, one pill two to four times a day for four months. While driving out of a parking lot, she had a generalized tonic-clonic seizure witnessed by her husband. Her husband controlled the car and prevented a crash. The seizure lasted for two minutes (during which it was noted that the patient bit her tongue) and was followed by a postictal period. She had had one seizure two years prior, which had been only partially evaluated (she had not received a CT scan at that time), and she was not treated. In addition, she had one sibling who had had a seizure at age 8, and the paternal grandparents were noted to have had seizures. She reported using alcohol only rarely. On evaluation, CT scan (non-contrast) was negative, oxygen saturation was 99 percent, toxicology screen was negative, pregnancy test was negative, and EEG was abnormal, "indicative of a potential underlying seizure disorder." Because of the prior history of seizures, we classified this as a possible sentinel event. (11649)

A 26-year-old male who had been using the product Ripped Fuel for approximately three years developed a headache that lasted approximately three days and then began experiencing seizures and was taken to the emergency room. While in the emergency department, he had a witnessed generalized tonic-clonic seizure. He had taken Ripped Fuel on the day of the event. Arterial blood gas and glucose were within normal limits. Drug screen was negative. Electrolytes were normal except for potassium of 3.2 and bicarbonate of 15.8. He had no history of medical illness, alcoholism, or serious injury. The family had no history of seizures. He had no further seizures over a three-hour period and was discharged home with referral to neurology. Two days later, he had another seizure and returned to the emergency department, where he was admitted to the hospital. Neurological consultation considered this case to be a complex partial seizure with generalized tonic-clonic seizure of new onset and to have a recent history suggestive of migraine headaches. Despite being given therapeutic doses of anti-seizure medications, he continued to have seizures to the point where he was placed in a Phenobarbital coma, requiring mechanical ventilation. After several weeks of a drug-induced coma, he was weaned off the Phenobarbital, but remained on anti-seizure medication and was left with a metabolic encephalopathy. He was transferred to a rehabilitation center. We classified this case as a possible sentinel event, because the clinical cause was quite complicated and from the records we had available we could not reach a more definitive conclusion. (13408)

A 30-year-old female was found by her husband to be moaning and making noises. She became limp and subsequently very confused. Paramedics were called and a blood glucose measured in the home was normal. She had been taking Metab-O-Lite for two to three months

for weight loss (the records are inconsistent on this point). She took one tablet before lunch and one tablet before dinner. Her last dose was on the day of the episode. She was on no medications, and had no personal or family history of seizures. She was seen in consultation by a neurologist. MRI with contrast was normal. An additional CT scan of the head, which was done without contrast, was interpreted as "negative." Serum electrolytes were normal, glucose was recorded in a dictated note as 19, but this is not commented on anywhere else in the notes and our presumption is that this is a typographical error. Serum calcium was normal, as was the complete blood count. The neurologist ordered an EEG, which showed an abnormality due to the presence of "some sharp waves emerging from the left hemisphere, mainly the parietal region." The neurologist's impression was that this was "most likely a seizure," and the patient was started and maintained on Dilantin. No further seizures were noted as of a follow-up three months after the event. We classified this case as a possible sentinel event, because it was not clear that the event was a seizure. (14275)

A 31-year-old female who was taking Thin Tabs (one tablet three times a day for approximately one month) developed a headache over her left eye, which became more severe after she took aspirin. The headache was followed by visual blurring, nausea, and vomiting, but no scintillations. She became tremulous, incoherent, and lethargic. She was taken by ambulance to the emergency room, where she had a generalized tonic-clonic seizure. In the emergency room, blood pressure was 165/107, pulse was 101, and respiratory rate was 24. Blood glucose was recorded as slightly elevated, and serum chemistries were normal. Sedimentation rate was normal. Non-contrast CT scan of the head was normal. Lumbar puncture was unremarkable. Gram stain was negative. Urine drug screen revealed amphetamines. She had no prior history of seizure. Physician's notes stated that the patient says she was "abusing" her diet pills, an assertion that was later denied in the medical record. Her medical history was remarkable for depression, for which she was being treated with Depakote (a drug used to treat seizure disorders, bipolar disorder, and schizophrenia), Trazodone, and Paxil (two antidepressants). It is also stated that she had an MRI, but those results were not in the material available for review. She had an electroencephalogram, which was normal, but which did not "entirely rule out a seizure disorder, as no Stage II sleep was seen, and a short record can miss intermittent phenomenon." Because of her EEG and in light of her taking other medications known to lower the seizure threshold, we classified this case as a possible sentinel event. (14571)

Insufficient Information

FDA Case—Ephedra

A 40-year-old female who had taken Ripped Fuel (two capsules, two times per day) for two days had a generalized tonic-clonic seizure (witnessed by her husband) while cooking dinner in her kitchen. She had no history of seizures. During the seizure, she fell, suffering a laceration to her head and was taken to the emergency department. At that time, glucose was 104, serum electrolytes were normal, and CT scan with and without contrast was normal. No report of an electroencephalogram was in the file. We classified this case as having insufficient information. (9747)

Psychiatric Symptoms

Sentinel Events

FDA Cases—Ephedra

A 21-year-old male took five to seven Nature's Nutrition-Formula One capsules in one day to stay alert while studying for final exams. He became psychotic and did not sleep for five days. A friend said he ran around campus looking like a homeless crazy person. The patient had no history of psychiatric or medical problems. (9509)

A 39-year-old female took Diet Now (tested by the manufacturer and said to contain 6 mg ephedra alkaloids per capsule, 12 mg per dose) for approximately one year at recommended doses. Her mother reports that the daughter experienced insomnia, hallucinations, psychosis, and delusions with the onset approximately one year after product initiation. She required hospitalization in a psychiatric facility for 40 days, with ongoing problems including terror, panic, and forgetfulness. She has now returned at work. (11678)

A 19-year-old female was taking Hydroxycut 2 pills twice a day to aid muscle definition and to speed metabolism. She reported dizziness and nausea two hours after use and began having violent outbursts, nightmares, poor mood, hot flashes, and fatigue. After a few days, she developed increased anger and rage and fought with boyfriend, mother, father, and sisters. She also tried to kill her boyfriend's sister and herself. After eight days of use, she developed a migraine and went to the emergency room. She then went home and picked up a knife, with homicidal intent, but was convinced to return to the hospital voluntarily. She was admitted for 18 hours and was readmitted later that day for a 72-hour involuntary hospitalization. Symptoms abated four days after Hydroxycut was discontinued. (13809)

A 29-year-old male took Xenadrine (two tablets twice per day) as a diet supplement for over six months. After six months of use, he was hospitalized three times for hyper-religiosity, paranoia, delusions, insomnia, and lack of concentration, and displayed some indication of the onset of bipolar disorder, but had no known history of prior mental health problems. Symptoms recurred twice more following use. (14529)

FDA Case—Ephedrine

A 16-year-old male took MaxAlert and Mini Thin for 11 months, often ingesting up to 40 tablets per day for weight loss and as a stimulant. The patient had episodes of aggressive behavior, irritability, tachycardia, insomnia, and violent and destructive behavior. When he visited a physician, it was noted that his symptoms coincided with an increase in dose of MaxAlert. No significant medical history and no history of other drug use were noted. We classified this as a sentinel event; however, we note the extraordinary use of product. (1855921)

Literature Case—Ephedra

A 45-year-old male who had taken an herbal dietary supplement labeled as ma huang daily for two months was brought to the emergency room by his wife when, after several weeks of using greater amounts, he began to display irritability, sleeplessness, and strange religious preoccupation. He had no medical or psychiatric history. His symptoms disappeared after brief treatment with Trazodone and discontinuation of ephedra. (48)

Literature Cases—Ephedrine

A 30-year-old female had taken Tedral (which contains ephedrine) for asthma for many years. She had no other medical problems and no history of psychiatric problems. Her mother had noticed a marked change in her behavior over the previous two years, which seemed to coincide with taking more Tedral than medically necessary. The patient became paranoid, illogical, and hallucinatory. A diagnosis of acute schizophrenic psychosis, either due to or aggravated by the abuse of ephedrine, was made. She was asked to stop taking Tedral but took it occasionally until persuaded by her family doctor to switch to cromoglycic acid. At two years follow-up, her symptoms had disappeared. (238)

A 59-year-old male who had taken ephedrine-containing products for over 25 years to treat asthma experienced auditory hallucinations, was delusional, and entered a woman's home, believing he was saving her from being tortured. At the time of the event, he had been taking ephedrine hydrochloride plus Bronchipax (ephedrine resinate 30mg; theophylline 40mg; salicylamide 250 mg) but had just doubled his daily ephedrine dose to 360 mg ephedrine plus Bronchipax. The patient had no history of psychiatric problems. The psychotic symptoms diminished 10–13 days after a reduction of the ephedrine dose. (285)

Possible Sentinel Events

FDA Cases—Ephedra

A 28-year-old female reportedly took one Slim NRG+ (ma huang) three times per day without incident for over 6 months and lost 30 pounds. After abruptly discontinuing use of the supplement, she was hospitalized for severe depression and a suicide attempt (gunshot wound to chest). She took no concomitant medications. Because no information regarding psychiatric or medical history was available, we classified this case as a possible sentinel event. (9751)

A 19-year-old man who took Ripped Fuel as directed (two capsules, three times per day) for three weeks was hospitalized with palpitations, increased blood pressure, and psychosis. He had no previous psychiatric problems or medical conditions. Because no information regarding psychiatric or medical history was available, we classified this case as a possible sentinel event. (11157)

A 13-year-old female took Nature's Nutrition-Formula One for approximately two weeks at recommended doses of approximately one tablet twice per day for weight loss. Her first symptoms were noted approximately one to two weeks after she began to use the product. She reported auditory hallucinations, disorientation to place, and withdrawal. Her symptoms endured for approximately two months. No information regarding medical or psychiatric history was included in the report, so we classified it as a possible sentinel event. (12372)

A 21-year-old male used Ripped Fuel as directed for two weeks. His parents reported personality changes such as nervousness, anger, and rage, and he went long periods without sleep. He had no previous psychiatric or medical problems. His parents reported he was sensitive to caffeine, which is included in the product. His symptoms stopped after the product was discontinued. (13005)

A 52-year-old female took Metab-O-Lite, two tablets three times per day for five months, for weight loss. She reported hallucinations, psychosis, delusions, and paranoia, which led to hospitalization in a state psychiatric facility. Her symptoms persisted for two to three days. She had a history of asthma and high blood pressure and no history of alcohol abuse. The report included a very confusing indication of a previous episode of hallucinations secondary to surgery or perhaps to Metab-O-Lite a few months earlier than the identified adverse event. (14436)

A 28-year-old female who took Metab-O-Lite (eight pills per day) for over six months for weight loss began to experience dizzy spells and headaches almost immediately after starting the supplement. She later began to experience chest tightness and a racing heart. Approximately one week after starting, she began to experience auditory hallucinations, delusions, and paranoia. Auditory hallucinations and delusions endured for over a year after discontinuing the product, thus we classified this as a possible sentinel event. (14528)

FDA Case—Ephedrine

A 31-year-old man used Max Alert for over four years, gradually increasing the dose until he was consuming 1,250 mg of ephedrine per day. He began to display psychotic behavior, including paranoia. Over four years, he was hospitalized three times, and at the time of report, was in a residential rehabilitation center for substance abuse treatment. The report states he had never used illicit substances and had no significant medical history. We classified this case as a possible sentinel event, but note the extraordinary dose of ephedrine. (1661966)

Literature Case—Ephedra

A 34-year-old male was brought to the emergency room after jumping from a second story window because he believed he was being chased. While taking ma huang over the previous nine days, he had experienced paranoid delusions and visual hallucinations. He had no history of mental illness. Medical history was not contained in the report. The patient was hospitalized for a number of weeks. After discontinuing ephedra, he remained well. The ephedrine content of the product was not noted in this case report; investigators contacted the manufacturer; however, they were unable or unwilling to disclose the amount of ephedrine in each tablet. (79)

Other Adverse Events

The FDA file contained reports of other adverse events associated with ephedra use. We briefly reviewed these reports in an attempt to more precisely establish the general nature of the adverse events, but we did not review them in more detail to determine whether they satisfied the three conditions necessary for a "sentinel event." Table 25 presents the list of other adverse events.

Metabolife File

The MIPER CD-ROMs contained 15,951 files. After removing duplicate, blank, and follow-up files, we had 18,502 cases for analysis, as indicated in Figure 18. Table 26 presents summary data regarding the key variables from our abstraction form on these cases. In 57 percent of cases, the consumer's age was not included. The majority of the remaining cases were reported by persons between the ages of 21 and 50, with a mean age of 38. In 66 percent of all cases, sex was not recorded. Of the remaining cases, 91 percent were female.

A tabulation of the symptoms showed that there were three deaths, 22 cases of myocardial infarction, three cases of cardiac arrest, 29 cases of stroke, two cases of brain hemorrhage, 46 cases of seizure, three cases of psychosis, and two cases of hallucinations. The files contained 111 cases of hospitalization in addition to those associated with the serious cases just listed. These hospitalizations were for a variety of reasons, but most were for cardiovascular-related symptoms.

The MIPER files for death, heart attack, cardiac arrest, stroke, seizure, and certain psychiatric events were all reexamined by the principal investigator and other physicians and are listed in Appendix 2 of this report. One case of death occurred as a result of "a brain hemorrhage," according to the notes. Another case involving a death contained a handwritten note that said, "wanted refund (sister's husb died)." The third case stated "cousin was taking Metabolife last yr, had stroke, died." No additional information for these cases is present. Two additional deaths, identified by Metabolife in a document entitled *77 'serious' AE's as identified by Metabolife* (see below), were not included in the MIPER CD-ROM we received. These additions bring the total number of Metabolife-related deaths to five. The cases of other serious events range in documentation from several sentences of clinical information related by the patient, letters from patients stating that they had a serious adverse event, to simply the words "heart attack" or something similar on a sheet of paper in the MIPER file. This level of documentation is insufficient to make judgments about the possible relation between ephedra use and the event. The largest proportions of case reports included symptoms of autonomic hyperactivity (14 percent of all cases) and gastrointestinal symptoms (26 percent of all cases). These data are compatible with the results of our meta-analysis of adverse events in placebo-controlled trials of ephedra and ephedrine, which demonstrated both autonomic hyperactivity and upper gastrointestinal symptoms to be causally related to use of ephedra or ephedrine.

As mentioned above, included with the material we received was a document (a sheaf of paper) entitled *77 'serious' AE's as identified by Metabolife*. This sheaf contained photocopies of the MIPER files judged by Metabolife to be the most serious in nature. These MIPER files included reports of three deaths. Two of these deaths had the MIPER number blacked out, were marked "privileged and confidential," were not found on the MIPER CD-ROM by our abstractors, and were not found using a modified MIPER CD-ROM that allowed text word searching (prepared for us by FDA).

The documentation on both cases consisted, as did many of the Metabolife files, of a printed version of an email. The first death was of a 45- to 55-year-old female, who was apparently initially healthy and continued to take Metabolife 356 for three weeks, despite symptoms of palpitations and a rapid pulse rate, until she suffered sudden death. An autopsy found "no conclusive cause of death." The email notes that toxicology studies are pending "to ascertain if ephedrine was present in her system at the time of death." No additional clinical information is available. The second case was that of a 30- to 40-year-old female who was found dead. According to her father, the autopsy "stated that the cause of death was of a cardiac nature of an unknown origin." Drug analysis found "only caffeine." No other clinical information was available.

Some cases identified by Metabolife as serious were not deemed so by us, whereas we considered a greater number of its cases to be serious than Metabolife did (we did agree on cases of death). For example, we identified six additional cases of myocardial infarction and nine additional cases of stroke. Table 27 compares the cases we identified as serious with those identified by Metabolife, along with a capsule explanation for the coding of discrepant cases.

Review of records with photocopies of medical information. The records varied greatly from detailed medical records to simply photocopies of medical bills. Table 28 contains a capsule description of each case and three numbering systems, because, as discussed in the Methods section, the medical records were numbered in three ways. The first column contains the number we assigned the records as we removed them from the shipping box. The second column contains the case number as listed on the *Index of Redacted Consumer Medical Records with Corresponding MIPER Numbers*. The third column contains the complaint case number from the *Listing of Key Complaint for the Metabolife Medical Records Submitted*. The fourth column contains the numbers for any related MIPER files that we identified or were identified by Metabolife on the Index. The column labeled "Notes" is our capsule description of what we received.

There were 12 cases with primarily cardiopulmonary symptoms (RAND ID cases 1, 13, 14, 16, 17, 20, 21, 23, 28, 29, 33, 43), two cases with neurologic symptoms (RAND ID cases 18, 38), two cases of seizure (RAND ID cases 32, 36), four cases of allergic reaction (RAND ID cases 2, 25, 26, 37), and 23 cases of miscellaneous symptoms (RAND ID cases 3, 4, 5, 6, 8, 9, 10, 11, 12, 15, 19, 22, 24, 27, 30, 31, 34, 35, 39, 40, 41, 42). There were no deaths, one case of myocardial infarction, no strokes, and no severe psychiatric events. The case of myocardial infarction (RAND ID case 23) was classified as a possible sentinel event, due to the presence of existing coronary artery disease. The two cases of seizure (RAND ID cases 32 and 36) were classified as sentinel events. Comparing these cases to the FDA Medwatch data contained in our Evidence Report demonstrates that neither the case of myocardial infarction nor the two cases of seizure are reported as sentinel or possible sentinel events in our analysis of the Medwatch file; thus, we are not double-counting these events.