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From J.D. Dupont
1-30-04

REVISIONS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 111

[Docket No. 1995N-0304]

RIN 0091-AA59

JAN 30 2004

**Final Rule Declaring Dietary Supplements Containing Ephedrine Alkaloids
Adulterated Because They Present an Unreasonable Risk**

AGENCY: Food and Drug Administration, HHS.

ACTION: Final Rule.

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

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

FOR FURTHER INFORMATION CONTACT: Wayne Amchin, Center for Food Safety and Applied Nutrition (HFS-007), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-6733.

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clinically significant effect on pulse or blood pressure, and produce no measurable alterations in myocardial function. A number of comments noted that changes in heart rate and blood pressure are transient and similar to those produced by exercise. Several comments stated that the effects of ephedra combined with caffeine on blood pressure are modest and generally subside over the first few days of use. Other comments stated that, although dietary supplements containing ephedrine alkaloids have a relatively high incidence of subjective and cardiovascular side effects with first use, the side effects diminish with continued use due to tachyphylaxis. Several comments noted that the literature, including the obesity studies we cited in the proposed rule (Ref. ~~36, 38-41~~ ^{49, 50}), indicated that tachyphylaxis sets in within a few days, at the most a few weeks, and results in a dramatic decrease in the likelihood of adverse events. Another comment suggested that pharmacological studies showed that peak ephedrine levels are reached within 1 to 4 days and that no further accumulation occurs thereafter. Another comment suggested that this fact means ephedrine alkaloids pose no risk of long-term toxicity.

One comment noted that ephedrine alkaloids are not toxic in the classic sense, that is, do not cause organ changes or damage to the metabolism. Other comments suggested that the available pathology data do not show any pattern consistent with ephedrine alkaloids as a cause of death.

(Response) We do not agree that ephedrine alkaloids pose no risk of adverse consequences. The suggestion that the cardiovascular effects of ephedrine alkaloids persist for only a few days is not supported by the Boozer et al. (2002) study (Ref. 49), which demonstrated a higher blood pressure (compared with placebo) at the end of one month of therapy. ^(Ref. 80a) This difference was observed when blood pressure was measured throughout the day, using

at each time point and careful attention to how blood pressure is measured. These design features are either lacking or not described in the publications cited by the comments summarized above, significantly limiting the trials' ability to detect any differences between the treatment and placebo groups with regard to blood pressure or heart rate. With regard to the timing of the measurement, the blood pressure measures appear to have been made at (or shortly after) the administration of the product containing ephedrine for almost all of the published trials. Absorption of the new dose would be minimal or incomplete and the dose taken the day before (8–12 hours earlier) would have been substantially removed from the circulation, given ephedrine's approximately 4-hour half-life. Blood levels of ephedrine would thus be at or near their lowest values of the day ("trough level"), a time when minimal effects on blood pressure would be anticipated. Measurements made only at trough level might well miss a significant effect on blood pressure that would have been seen at or near peak concentrations of ephedrine. Thus, although some published studies on the cardiovascular effects of ephedrine (especially blood pressure) over a period of weeks or months have reported little or no effect of ephedrine on blood pressure and a variable effect on heart rate, these studies are severely limited in their ability to establish safety, such that the true effects of ephedrine on heart rate and blood pressure cannot have been adequately assessed.

We do not agree with the comments that state that ephedrine alkaloids are not toxic because they do not induce specific organ pathology. Persistently elevated blood pressure can result in defined cardiovascular toxicity (Ref. 24, 29, 35), as can ephedrine's sympathomimetic effects in people with coronary artery disease or heart failure, but the kinds of damage seen in humans from

become of the
clinical trial
design
limitations.
(Refs. 81a,
81b, 81c)

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

VIII A. 5. a. i
 In section ~~xx~~ we discuss in detail how we estimated rates of adverse event reporting for purposes of our impact analysis for this final rule. *Note this is different from last change due to new #s in Econ section*

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

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

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

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

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

VIII. Analysis of Impacts

A. Benefit-Cost Analysis

→ 1. Introduction

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

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

2 Regulatory Options

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

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

3. Summary of Conclusions

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

4. Option One—Take No New Regulatory Action

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

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

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

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

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

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

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

i. Use of AERs in Estimating Benefits and Baseline Number of AERs

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

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

ii Valuing reductions in adverse events

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

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

iii *Serious vs. minor adverse events*

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

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

 *Risks of Substitutes and Weight Regain*

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

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

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

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

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

✓ *Risks of Certain Dietary Supplements Containing Ephedrine Alkaloids* ~~from the~~
~~Market~~

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

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

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

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

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

their ephedra-based products and replaced them with reformulated products to avoid the high legal and insurance costs associated with dietary supplements containing ephedrine alkaloids (Ref. 146).

5. Option Three—Require the 2003 Proposed Warning Statement

a. *Benefits of Requiring the 2003 Proposed Warning Statement*

1. *Comparison to removing dietary supplements containing ephedrine alkaloids from the market*

In the analysis of the 1997 proposed rule, we noted that estimating the benefit of limiting our regulatory action to requiring the 1997 proposed warning statement involved a potentially controversial value judgment about how one evaluates risks that consumers voluntarily accept in the presence of adequate warning statements (62 FR 30711). Our analysis of a mandatory warning statement is further complicated by the fact that the labels of most dietary supplements containing ephedrine alkaloids already bear warning statements.

(Comment 82) One perspective that we discussed in the analysis of the proposed rule was that adverse events that occur despite the presence of adequate warning statements are not social costs but are instead private costs that reflect informed decisions about the private benefits and costs of using these products. A number of comments agreed with this perspective. One comment argued that consumers have a responsibility to read and follow warnings and instructions for use on products that they consume. Some comments suggested that we should expect consumers to read and follow warning statements, and we should not hold manufacturers liable if consumers fail to do so. One comment argued that we have adopted that viewpoint in other cases involving products that can produce severe adverse effects. Some

at least some consumers to change their demand so as to incorporate the risk, then the warning label could reduce adverse events and generate net social benefits. The likelihood of that outcome depends on the effectiveness of current warning statements and of warning statements in general. One consideration that suggests that consumers fail to incorporate, at least in part, the probability of adverse events into their market behavior is that some consumers do not know they have the underlying conditions discussed in warning statements.

ii Comparison to Existing Warning Statements

In economic terms, the benefit of changing a warning statement is the value that consumers place on the change in the information available on product labels. If we had information on how consumers value different warning statements, then we would not need to consider the impact of changing the warning statements on adverse events. Without that information, we must infer the value from the adverse health effects that changing the warning statement would eliminate. This value represents the minimum value of changing the warning statements: consumers who change their behavior in response to the change in warning statements would presumably be willing to pay the amount that they saved in health costs and lost utility because of that change in warning statements, but some consumers might value the information even though they do not change their behavior. Because the information value for consumers who do not change their behavior is likely to be small, the value of the eliminated adverse events is probably a close approximation to the value of changing the warning statements. Therefore, we have based our analysis on estimating the impact on adverse events of

changing the warning statements from the existing voluntary industry warning statements to the proposed mandatory warning statement.

Effectiveness of Warning Statements in Eliminating Adverse Events

In the analysis of the proposed rule, we estimated that the warning statement that we proposed in 1997 would reduce the estimated number of annual adverse events caused by dietary supplements containing ephedrine alkaloids by 0 to 15 percent (62 FR 30712).

(Comment 83) A number of comments addressed this estimate. One comment suggested that the estimated impact was too low and noted that a recent study showed that almost 70 percent of adults read product labels every time they use a product. However, another comment argued that warning statements would probably be ineffective because most consumers do not read product labels. This comment noted that there is no evidence that warning labels on alcohol and tobacco products reduced consumption of those products. Other comments simply pointed out that warning statements might not eliminate all adverse events, because some consumers might not read or follow them. One comment provided a number of reasons why warning statements might be ineffective at reducing adverse events (e.g. many consumers do not read labels for OTC drugs and would be even less likely to do so for dietary supplements, many consumers base their usage patterns on suggestions read in magazines rather than on label information, many consumers believe consuming more of a dietary supplement makes it more effective). Another comment noted that we appeared to infer the ostensible benefit of warning statements rather than demonstrating their effectiveness through carefully conducted clinical trials. This comment also argued that warning statements would not be useful for consumers with unrecognized

to every year after the first year. Benefits for the first year would be lower because our proposed rule would have allowed firms up to six months to comply with the warning statement requirements. We do not know the actual rate at which firms would come into compliance during the initial six months after publication of a rule finalizing the proposed warning statement requirements. To simplify the analysis, we assume that it would take all firms six months to comply with such a rule. Under this assumption, the benefits in the first year would be half those of every year after the first year. In the summary of regulating options and Table 8, we use the range \$0 to \$20 million for annual benefits (excluding the first year) because it is inconsistent with the presentation of the other options.

TABLE 5.—ANNUAL BENEFITS OF OPTION THREE (REQUIRE THE 2003 PROPOSED WARNING STATEMENT) BASED ON ELIMINATING 0 TO 15 PERCENT OF THE SENTINEL AND POSSIBLE SENTINEL EVENTS

Type	Number	QALY Loss Per Case	Medical Costs per Case
Death	0.0 to 0.2	NA (used VSL)	\$25,742
MI (heart attack)	0.0 to 0.2	0.29	\$30,586
CVA (stroke)	0.0 to 0.3	0.2	\$20,898
Other Cardiovascular (e.g. Cardiomyopathy, Ventricular Tachycardia)	0.0	0.29	\$30,586
Other Neurological (e.g. Transient Ischemic Attack)	0.0	minimal	\$13,212
Seizure	0.0 to 0.1	minimal	\$11,812
Psychiatric	0.0 to 0.2	minimal	\$6,927

Table 6.—Annual Benefits of Option Three (Require the 2003 Proposed Warning Statement) Based on Alternative Assumptions of Reporting Rates, rounded to \$ millions

Value of Avoiding Fatal Cases and QALY Losses	Adverse Event Reporting Rate		
	10 percent	50 percent	100 percent
\$ per fatal case = \$5 million\$ per QALY = \$100,000 \$0 to \$11 \$0 to \$2 \$0 to \$1			
\$ per fatal case = \$6.5 million\$ per QALY = \$100,000 \$0 to \$14 \$0 to \$3 \$0 to \$1			
\$ per fatal case = \$5 million\$ per QALY = \$300,000 \$0 to \$14 \$0 to \$3 \$0 to \$1.			
\$ per fatal case = \$6.5 million\$ per QALY = \$300,000 \$0 to \$17 \$0 to \$3 \$0 to \$2.			
\$ per fatal case = \$6.5 million\$ per QALY = \$500,000 \$0 to \$20 \$0 to \$4 \$0 to \$2			

c. Costs of Requiring the 2003 Proposed Warning Statement

Label Costs

(Comment 86) Some comments said that the proposed PDP or non-PDP warning statements are too long to fit on the labels of most dietary supplement products. One comment noted that firms package many “traditional style extracts” in containers that have a maximum label size of 1.75 x 3.75 inches,

labels of dietary supplements containing ephedrine alkaloids to be \$3 million to \$6 million, which rounds to approximately \$0 million per year (i.e. less than \$500,000 per year) when annualized over 20 years at 3 percent and approximately \$0 million to \$1 million per year when annualized over 20 years at 7 percent. We are unable to quantify potential recurring countervailing health costs. We estimate the recurring annual benefit to be \$0 to \$20 million, depending on the reporting rate for adverse events, and the method used to value those events. Therefore, we estimate the annual net benefit of this option to be -\$1 million to \$20 million. In the long run, this option would probably generate net benefits, for two reasons: First, the benefits recur annually and any non-zero level of benefits will eventually surpass the one-time labeling cost. Second, as we discussed above, the recurring countervailing health costs are unlikely to exceed the recurring health benefits.

7. Option Four—Require the proposed warning statement, but modify it or require it only on certain products^{a.} Require Warning Only for Certain Products

We discussed a number of comments under Option Two that claimed that certain dietary supplements containing ephedrine alkaloids do not pose any health risks. That discussion is also relevant in the context of exempting certain products from the proposed warning statement. The summary of those comments and our response is the same as under Option Two above. For example, one comment suggested that warning statements are unnecessary for herbal products that firms distribute to “healthcare professionals,” including members of the American Herbalists Guild. We do not have sufficient information to estimate the impact of exempting products based on patterns of distribution or other product characteristics.

b. *Placement and Format of Warning Statement*

RAND report did not support the need for a black box type of warning statement. Some comments suggested that we give manufacturers greater leeway with respect to the format of the warning statement. Other comments supported the requirement that firms set off the warning statement in a box graphic. One comment suggested that we require firms to set off the warning statement in a brightly colored or neon box instead of in a black box.

(Response) The proposed warning statement is consistent with current research on effective warning statements. Eliminating the box graphic would probably not significantly reduce relabeling costs. However, it might reduce the visibility of the warning statement, which would reduce the distributive impacts of the rule as well as the rule's potential health benefits. We have no information establishing that colored boxes are more effective than black boxes. Depending on the background color of the label, colored boxes may reduce the color contrast between the border and the background, which would decrease visibility of the warning statement. In addition, requiring colored boxes would increase labeling costs because some existing labels are not printed in colors.

C. Content of PDP warning

(Comment 93) Some comments suggested that we revise the proposed PDP warning statement in various other ways. One comment argued that there was no evidence that "whole-herb products" containing ephedrine alkaloids have been associated with heart attack, stroke, seizure, or death, so that the proposed PDP warning statement would be inappropriate for those products. This comment suggested that we revise the PDP statement so that it simply informs consumers that a product contains ephedrine alkaloids and directs them to a warning statement elsewhere on the label. A number of comments argued that

ephedrine alkaloids cause these types of adverse events. One comment suggested that if we refer to these types of adverse events in the warning statement, then we should include a qualifying statement explaining that no one has established a causal link between these types of adverse events and ephedrine alkaloids. This comment also suggested that we indicate in the warning statement that reports of serious adverse events are extremely rare.

(Response) Although the information in the proposed warning statement is factually correct because some people have reported the specified adverse events after consuming ephedrine alkaloids, some consumers might interpret the phrase “have been reported” to mean that a proven causal relationship exists between the consumption of the ephedrine alkaloids and the reported adverse events. This perception could generate additional costs in terms of lost consumer utility because some consumers who would choose not to consume these products if a proven causal relationship existed might choose to continue to consume these products if a causal relationship were only possible or even likely. One way to reduce potential misperceptions would be to add a disclaimer to the label, explaining that the causal relationship between ephedrine alkaloids and these adverse events may be uncertain. This additional material might either decrease or increase the demand for these products, and consumers are generally less likely to respond to a longer, qualified warning statement, than to a shorter, non-qualified warning statement. The comments did not provide sufficient information to establish that adding this type of clarification to the warning would increase the benefits of the warning statement.

d. *Content of non-PDP warning statement*

Conclusions on benefits and costs of modifying the proposed warning statement or requiring it only for certain products

Requiring a warning statement for certain products only would reduce costs and distributional effects and might reduce benefits compared with Option 3 (all comparisons in this section are with Option 3). Eliminating the PDP warning statement or eliminating the box graphic would have little effect on costs but would reduce distributional effects and probably also reduce benefits. Requiring a colored box graphic instead of a black and white box graphic would increase costs and possibly increase distributional effects and benefits. Revising the content of the warning statements would have little effect on costs but might increase or decrease distributional effects and benefits, depending on the revision. We have insufficient information to quantify these possible impacts, so we are unable to provide a summary estimate of the costs and benefits of this option.

g Option Five—Generate additional information or take some other action other than removing dietary supplements containing ephedrine alkaloids from the market or requiring warning statements

(Comment 97) One comment argued that we have no controlled epidemiological studies that support an association between ephedrine alkaloids and stroke, seizure, or myocardial infarction. Other comments noted that RAND said in its report that it was unable to establish that ephedrine alkaloids caused adverse events and that RAND recommended that someone perform a controlled clinical study to address the issue. Another comment noted that Haller and Benowitz (2000) said that their approach did not establish that ephedrine alkaloids caused adverse events and suggested that someone do a large scale case control study to quantitatively determine the

distributors. Another comment suggested that we develop a Level 1 guidance document rather than taking regulatory action.

(Response) The comments did not provide sufficient information to establish that spending additional resources on enforcement of existing regulations or on promulgating a Level 1 guidance document would generate greater net benefits than promulgating this final rule. Following guidance documents is strictly voluntary. The fact that some manufacturers continue to produce dietary supplements containing ephedrine alkaloids despite ongoing and well-publicized concerns about the safety of such products suggests that voluntary guidance documents are unlikely to have a significant effect.

Q. Benefit-Cost Analysis: Summary

Removing dietary supplements containing ephedrine alkaloids from the market (i.e. taking this final action) will generate estimated benefits of between \$43 million and \$132 million per year. We used the following assumptions to calculate this range of benefits: a 10 percent reporting rate for adverse events, no potentially countervailing health effects from the use of substitute products and other weight loss alternatives, no countervailing health effects from potentially foregone weight loss, and the fact that consumers do not already understand and incorporate the risks posed by these products in their consumption decisions. Including the impact of substitute products and activities could reduce the rule's health benefit considerably, possibly to \$0 per year, although that is unlikely. These countervailing effects may occur because this rule will not affect the underlying demand for products having functional characteristics similar to ephedrine alkaloids, and it is likely that products having similar functional characteristics may contain similar types of ingredients that may pose similar types of health risks. The range of benefits

already understand and voluntarily accept the risks posed by these products, to an annual net social benefit of \$125 million, if there are no countervailing health risks and consumers do not already understand and accept the known and potential risks.

TABLE 8.—SUMMARY OF OPTIONS (ROUNDED TO \$ MILLIONS)

Option	Annual Cost	Annual Benefit	Net
1. Take No New Regulatory Action (baseline)	\$0	\$0	\$0
2a. Remove dietary supplements containing ephedrine alkaloids from the market (if consumer behavior does not already incorporate risk)	\$7 to \$90	\$43 to \$132	- \$47 to \$125
2b. Remove dietary supplements containing ephedrine alkaloids from the market (if consumer behavior already incorporates risk)	\$7 to \$90	\$0	- \$90 to - \$7
3. Require 2003 Warning Statement	\$0 to \$1	\$0 to \$20	- \$1 to \$20
4. Require Warning Statement, but modify it or require only on certain products	NA	NA	NA
5. Generate Additional Info or take some action other than removal or warning statements	unknown	unknown	unknown

B Small Entity Analysis

We have examined the economic implications of this final rule as required by the Regulatory Flexibility Act (5 U.S.C. §§ 601–612).  a rule has a significant economic impact on a substantial number of small entities, the Regulatory Flexibility Act requires us to analyze regulatory options that would lessen the economic effect of the rule on small entities. We find that this final rule would have a significant economic impact on a substantial number of small entities.

(Comment 99) Some comments addressed our estimate of the number of small firms in the analysis of the proposed rule. Some comments argued that we had ignored a large number of independent small distributors in the analysis of the proposed rule. One comment suggested we revisit our analysis of the impact of the rule on small businesses. One comment suggested we obtain information on the impact of the rule on small entities by opening a dialogue with industry associations.

(Response) We have revisited and revised our estimate of the number of firms based on a database of dietary supplement products that the Research Triangle Institute compiled under contract to FDA after publication of the