of the dietary supplements containing ephedrine alkaloids. This range is based on the fact that some premium must exist if consumers prefer these products to alternatives. We selected 1 percent as a lower bound because we did not find any large price differences between products containing ephedrine alkaloids and those that did not contain ephedrine alkaloids. Of course, it is possible that current consumers place a much higher premium on products containing ephedrine alkaloids than consumers who have already switched to alternatives. To allow for that possibility, we selected 10 percent (a substantial premium) as the upper bound of the range. Current market prices do not provide sufficient information for a more precise estimate. This estimate of the utility loss assumes that consumers do not incorporate the expected utility losses from potential adverse events in their willingness to pay for dietary supplements containing ephedrine alkaloids. If consumers already incorporate this information in their purchasing decisions, then it would be inappropriate to compare the value of the health benefits to the estimated utility losses for consumers using willingness to pay because the willingness to pay would already account for any adverse health effects. In that case, the estimated utility loss from the removal of these products from the market would represent the full net loss of utility.

A recent article estimated that the sales of "herbal products" containing ephedra accounted for between 4.3 percent and 13.5 percent of the sales for all herbal products (Ref. 135). The article did not define "herbal products," but it noted that their use of the phrase "herbal products" included products that a natural products information company had classified as "vitamins/supplements" and "grocery" items rather than as "herbal products" (Ref. 147). Therefore, these estimates may have included products other than dietary

supplements. Another source argued that the estimates presented in the article that we discussed previously in this paragraph did not include all relevant products. The source claimed that more comprehensive data from the Nutrition Business Journal showed that the sales of products containing herbal ephedra accounted for 33 percent of the total sales of all herbal products and 7.5 percent of the total sales of dietary supplements (Ref. 148). Both of these articles apparently dealt only with products that contained herbal ephedra. Ephedrine alkaloids are also contained in a number of different plants, including *Sida cordifolia* L., and *Pinellia ternata* (Thunb.) Makino. Therefore, these articles may have underestimated the number of products that contained ephedrine alkaloids. These articles did not present actual sales figures for herbal products, dietary supplements, or products containing ephedra. However, the Nutritional Business Journal estimated that the sales of all dietary supplements nd all herbal dietary supplements in 2002 were $18 billion and $4.3 billion, respectively (Ref. 149). If one assumes that "herbal dietary supplements" corresponds to "herbal products," then total sales of dietary supplements containing ephedrine alkaloids would be $185 million to $1,419 million.

In an effort to reduce this range, we estimated the sales of these products based on a recent survey that showed that 2 million consumers used these products at some point during a given week (Ref. 150). We assumed that consumers who used these products at some point during a given week probably used the products every day during that week, because most of the labels we have examined say that the product should be taken daily, or several times per day. We also assumed that the particular week under study was comparable to any other week. Therefore, we assumed that 2 million consumers use these supplements per day. We then multiplied this number

of consumers by the average daily cost of these supplements, which we estimated from a sample of 30 dietary supplements containing ephedrine-alkaloids that we found on the Internet. Based on the recommended intake levels appearing on the labels of these products, the corresponding estimated total sales per year is $559 million to $806 million. The costs in the first year after publication of the rule would be slightly different from the cost in every subsequent year because the effective date is 60 days after the publication date of the final rule. Therefore, the utility losses in the first year will be 5/6 (or 83 percent) of the losses of every subsequent year. To simplify the discussion, we use the benefits for every year after the first year in all summary discussions.

Earlier, we assumed that the consumer utility loss from switching from an ephedra-based product to the next closest substitute would be from 1 percent to 10 percent of the sales price at the current level of consumption. Under this assumption and our estimate of total sales, the consumer utility loss associated with removing dietary supplements containing ephedrine alkaloids from the market would be $6 million to $81 million per year. The loss of consumer utility would probably decline over time as consumers find more substitute products and as producers develop new, more acceptable substitute products. Eventually, consumer substitutions and product development could drive this cost to zero. We have insufficient information to estimate the rate at which this cost would decline over time.

In the analysis of the June 1997 proposal, we estimated relabeling costs of $3 million to $60 million and product reformulation costs of $0 million to $25 million, for a total cost for these two activities of $3 million to $85 million (62 FR 30678 at 30709). We did not receive any comments on these

estimates. We have, however, revised the analysis to incorporate a new model for estimating reformulation costs that we developed after publication of the proposed rule (Ref. 151). According to that model, reformulation costs with a 12-month reformulation period would be $7 million to $78 million. In deriving that figure, we assume that reformulating dietary supplements would not be as complicated as reformulating most other types of food and cosmetics. In particular, we assume that reformulating dietary supplements would include the following cost generating activities: Idea generation, product research, analytic testing, packaging development, plant trials, startup, and lost inventory. We assume that reformulating dietary supplements would not include the following types of cost generating activities: Process development, coordinating activities, consumer tests, shelf life studies, any type of safety studies, and market tests. If all of these other steps were involved, then estimated reformulation costs for a 12-month reformulation period would be $22 million to $142 million. We assume that 6 months is the most likely time period for reformulation if dietary supplements containing ephedrine alkaloids are removed from the market. Although the effective date of this rule is 60 days after the publication date, we do not expect that many firms will try to condense the reformulation process into a 60-day period. Some firms may have already done some of the preliminary work for reformulation. Other firms might need to withdraw their product from the market in the period between the effective date and the date at which they complete their reformulation. FDA's reformulation cost model does not address costs for a reformulation time of 6 months, so we extrapolated the costs based on the proportionate change in cost that would result from halving the reformulation time from 24 months to 12 months. Under that extrapolation, we estimate that reformulation costs

for a 6-month reformulation period would be $10 million to $100 million. We annualize these estimated costs over 20 years at an interest rate of 3 percent to convert these one-time costs to a yearly cost of $1 million to $7 million. Annualizing these costs over 20 years at an interest rate of 7 percent gives an annual cost of $1 million to $9 million.

We summarize the annual costs of this option in table 3 of this document. We compare the benefits and costs of this option in table 4 of this document. To obtain the higher bound estimate of net benefits, we start with the higher bound estimate of benefits and subtract the lower bound estimates of costs. To obtain the lower bound estimate of net benefits, we start with the lower bound estimate of costs and subtract the higher bound estimate of costs. If consumer behavior already incorporates health risks, then utility costs would already be net of health benefits. In that case, the net impact of this rule is simply the total costs.

TABLE 3.—ANNUAL COSTS OF OPTION TWO (REMOVING DIETARY SUPPLEMENT CONTAINING EPHEDRINE ALKALOIDS FROM THE MARKET) ROUNDED TO $ MILLIONS

Type of Cost	Cost (rounded to $ millions)
Utility Losses for Consumers	$6 to $81
Product Reformulation	$1 to $9

TABLE 4.—ANNUAL SOCIAL BENEFITS AND COSTS OF OPTION TWO (REMOVING DIETARY SUPPLEMENT CONTAINING EPHEDRINE ALKALOIDS FROM THE MARKET) ROUNDED TO $ MILLIONS

Type of Benefit or Cost	Benefit or Cost (rounded to $ millions)
Health Benefits (for 10 percent reporting rate)	$43 to $132
Cost of Utility Losses for Consumers	$6 to $81
Cost of Product Reformulation	$1 to $9
Net Effect (if consumer behavior does not already incorporate health risks)	-$47 to $125
Net Effect (if consumer behavior already incorporates health risks)	-$90 to -$7

d. *Distributional issues and impact on industry.* In the analysis of the June 1997 proposal, we estimated that removing dietary supplements containing ephedrine alkaloids from the market would reduce the sales of dietary supplements containing ephedrine alkaloids by between $200 million and $230 million per year (62 FR 30678 at 30710). We discussed reduced sales because, in that analysis, we characterized a reformulated product as the same

product as before reformulation for purposes of describing the impact of the proposed action (although the reformulated products would obviously not be the same as the products they replaced). We did not receive comments that would require us to change those estimates. However, we have revised the analysis to reflect the fact that the effect on accounting profit is a more appropriate way to conceptualize the potential distributional impact than reduced sales. We can use the same information that we used to estimate consumer utility losses to consider the likely effect on the profits of firms that currently produce dietary supplements containing ephedrine alkaloids. In 2001, the average accounting profit for all Fortune 500 companies was about 5 percent of revenue, and some pharmaceutical firms had profit rates as high as 19 percent of revenue (Ref. 150). Profit rates for firms in the dietary supplement industry are probably toward the low end of this scale because of the low barriers to entry for this industry. Therefore, we assume that the profit rate for dietary supplement manufacturers is about 5 percent of total sales. As we discussed previously, press accounts suggest that manufacturers that have reformulated their dietary supplements to eliminate ephedrine alkaloids have experienced declines in sales ranging from about one-third to no decline in sales. We previously estimated total sales to be $559 million to $806 million. Therefore, we estimate that sales may decrease by $0 to $269 million per year. Assuming that the profit rate is 5 percent of sales, removing dietary supplements containing ephedrine alkaloids from the market would generate accounting profit losses of $0 to $13 million per year. We classify this impact as a transfer and not a social cost because removing dietary supplements containing ephedrine alkaloids from the market would increase the profits of firms that produce and distribute substitute products. If these

other firms also have an average profit rate of 5 percent of sales, then the profit gained by these companies would also equal $0 to $13 million per year.

In addition to causing a potential reduction in profits for firms currently producing dietary supplements containing ephedrine alkaloids, removing dietary supplements containing ephedrine alkaloids from the market might also generate some countervailing transfers through the elimination of insurance costs and lawsuits associated with products containing ephedrine alkaloids. Eliminating legal fees and court costs would also generate social benefits. Of course, if reformulated products were eventually found to pose health risks comparable to those found for ephedra-based products, then these effects (i.e., the elimination of insurance and legal costs) would eventually decrease to zero. A recent press report found that ephedra manufacturers or distributors have settled 33 cases since 1994 and that an additional 42 cases were pending (Ref. 152). This represents 75 cases over 9 years, or about 8 cases per year. Recent awards for cases that have gone to court have ranged from $2.5 million to $13 million (Refs. 152 and 153). The figures reported in the media for cases that were settled out of court were considerably lower. One such case was settled out of court for $25,000 (Ref. 152). If removing dietary supplements containing ephedrine alkaloids from the market eliminated 8 cases per year, then it would decrease transfer payments from firms to consumers by between $0.2 million per year, if all cases were settled out of court, and $104 million per year, if all cases were lost in court at the high end of the range of legal penalties.

One company noted in 2002 that its product-liability insurance increased by $2.1 million from 2001 to 2002 (Ref. 146). If all 30 manufacturers saw this increase in insurance premiums, then the total increase in insurance premiums

would be $60 million. Some of the independent distributors might also face higher insurance rates, but we have insufficient information to estimate those costs. Insurance rates would not necessarily increase at this same rate in the future, and they could decrease. Therefore, we will assume that this adjustment in insurance rates reflects a one-time adjustment in the perceived liability risks associated with these products. If these higher premiums were unnecessary for reformulated products, then removing dietary supplements containing ephedrine alkaloids from the market would generate a one-time reduction in private costs of $60 million. However, if reformulated products were eventually shown to pose risks comparable to those for ephedra-based products, then insurance rates might increase to a comparable level for these products.

The uncertainty ranges associated with the potential transfers of accounting profits make it impossible to estimate the impact of removing dietary supplements containing ephedrine alkaloids from the market on the firms that currently produce and distribute dietary supplements containing ephedrine alkaloids. Firms that are unable or unwilling to produce or sell substitute products would suffer losses, and firms that are able and willing to produce or sell substitutes might not suffer decreases in profits. Indeed, media reports suggest that many firms have already voluntarily withdrawn 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).

6. Option Three—Require the 2003 Proposed Warning Statement

a. *Benefits of requiring the 2003 proposed warning statement comparison to removing dietary supplements.*

i. Containing ephedrine alkaloids from the market. In the analysis of the June 1997 proposal, 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 30678 at 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 June 1997 proposal 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 comments from consumers argued that we should take no regulatory action other than requiring a warning statement because that approach would allow consumers to decide whether or not to assume the risks associated with these products. One comment pointed out that a recent report on the safety of ephedrine alkaloids that was sponsored by industry endorsed this perspective, as expressed in the following quote: "As the law appropriately suggests, the FDA cannot assume responsibility for protecting the public from themselves,

if they choose to use this or any other product at higher than recommended levels or otherwise misuse properly labeled products."

The other perspective on warning statements that we discussed in the analysis of the June 1997 proposal was that adverse events that occur despite the presence of adequate warning statements represent social costs. Under this perspective, requiring a warning statement would not be a sufficient regulatory action unless it actually caused consumers to change their behavior so as to eliminate any adverse events associated with these products. Some comments supported this perspective by arguing that warning statements are inappropriate or inadequate because they probably would not significantly reduce the number of adverse events among all or some subset of consumers.

(Response) In the analysis of removing dietary supplements containing ephedrine alkaloids from the market, we concluded that removing dietary supplements containing ephedrine alkaloids from the market would generate net social benefits if consumers fail to incorporate the probability of adverse events into their demand for those products. Our assessment of the effects of a warning statement hinges on the same uncertainty. If consumers do not fully incorporate the risk of adverse events into their demand for products containing ephedrine alkaloids, and if the proposed warning label would cause 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.

iii. *Effectiveness of warning statements in eliminating adverse events.* In the analysis of the June 1997 proposal, 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 30678 at 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 medical conditions that might predispose them to adverse reactions caused by ephedrine alkaloids, such as hypertension, hyperthyroidism, vascular malformations of the brain, and subclinical cardiac arrhythmias. One comment suggested that the proposed warning statement was too long to be effective. This comment claimed that the necessary print size and spacing would discourage some consumers from reading the warning statement.

(Response) These comments did not provide sufficient information to allow us to change our estimate of the effectiveness of the warning statement that we originally proposed in 1997 and revised in 2003. The comments that noted that warning statements might not eliminate all adverse events are consistent with the assumption that warning statements would eliminate 0 to 15 percent of the adverse events. The comment that noted a study that showed 70 percent of consumers read product labels every time they purchase a product did not provide a reference for that study, but the reported results are consistent with other studies. The FDA 2002 Health and Diet Survey found that 80 percent of nonvitamin/mineral supplement users reported that they used product labels to find out if there were side effects or drug interactions associated with a product or if anyone should avoid the product. A survey of consumer use of dietary supplements by Prevention Magazine found that the following percentages of herbal remedy shoppers reported looking for the following types of information: 72 percent for possible side effects; 70 percent for warnings for people not to take the supplement, e.g. pregnant women; 65 percent for warnings about possible interactions with prescription medicines; and 59 percent for warnings about possible interactions with OTC products (Ref. 154). However, consumers who read warning statements will not necessarily change their behavior. A 2002 recent survey of consumers who have recently taken OTC pain medications found that 84 percent read at least some of the label the first time they took a product but that 44 percent said they took more than the recommended dosage, despite the warnings on the label (Ref. 155). In general, most of the literature on warning statements has not focused on product purchase or use pattern decisions but on issues such as comprehension, awareness, and believability (Ref. 156). Some articles have

found that alcohol warning statements have had little or no impact on behavior (Ref. 157). However, these results do not necessarily hold for the proposed warning statement because the effectiveness of warning statements varies with a number of considerations, including the content and format of the warning and the characteristics of the consumers reading the warning. Thus, this literature does not provide a basis for revising our assumption that the proposed warning statement will reduce adverse events by 0 to 15 percent. However, the fact that most dietary supplements already bear extensive warning statements suggests that 15 percent is probably an upper bound and that a value closer to 0 percent is probably more likely.

(Comment 84) Some comments argued that the proposed warning statement would probably have little effect on the number of adverse events because many dietary supplements that contain ephedrine alkaloids already bear warning statements. One comment argued that some existing warning statements fully and accurately describe the potential for adverse effects and thereby satisfy the objectives of the proposed warning statement. One comment argued that some existing warning statements are more complete than the proposed warning statement. However, one comment said that the proposed warning statement would probably be more effective than existing warning statements because existing warnings do not alert consumers to avoid taking multiple products containing ephedrine alkaloids at the same time.

(Response) To address these comments, we reviewed and compared the labels of forty dietary supplements containing ephedrine alkaloids that we collected between March 20 and May 30, 2001, and also compared the number of adverse reports received during the period January 2000 to January 2004 as warning labels appeared on certain dietary supplements. (Ref. 158) All of

the product labels bore some sort of warning statement. Most warning statements had many of the same basic elements as the proposed warning statement. For example, most existing warnings listed various conditions under which consumers should not take the product, various conditions under which consumers should see a health care provider before taking the product, and side effects or symptoms that should lead consumers to consult with a health care provider. However, the specific content of the various elements varied quite a bit both among existing warning statements and between existing warning statements and the proposed warning statement. Some elements of the proposed warning statement were common in existing warning statements; other elements were less common. For example, none of the existing product labels carried a PDP warning statement. In contrast, most product labels carried some sort of warning for people who had previously experienced heart problems. In addition, parts of some existing warnings were more strongly worded than the corresponding parts of the proposed warning. In other cases, parts of the proposed warning were more strongly worded than the corresponding parts of existing labels. Our label comparison did not support the notion that the proposed warning statement would have no effect because it was identical to existing warning statements. The comparison did suggest that the proposed warning statement is similar in many respects to existing warning statements, and that the proposed warning statement might not reduce adverse events very much. This result is consistent with the assumption that the proposed warning statement might eliminate between 0 and 15 percent of adverse events.

(Comment 85) Some comments argued that the proposed warning statement would be ineffective because some States already require warning

statements, and the presence of multiple warning statements would confuse consumers.

(Response) Multiple warning statements might reduce the impact of the proposed warning statement. However, many different warning statements might be more effective than one or a few. The comments did not provide sufficient information to enable us to revise our estimate of the effectiveness of the proposed warning statement based on the possibility that some products might face multiple labeling requirements.

b. *Revised benefit estimates.* When we revise the analysis as described previously, we obtain the estimated benefits shown in table 5 of this document. The assumption underlying the table is that the proposed warning statement would cause some proportion of consumers to incorporate the risks from dietary supplements containing ephedrine alkaloids into their demand for these products. Some proportion of those consumers (0 to 15 percent) would cease using those products, which would reduce the number of adverse events by a like percentage. The benefits would therefore be some percentage (between 0 and 15 percent) of the benefits of removing dietary supplements containing ephedrine alkaloids from the market. The results presented in table 5 of this document apply 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 6 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 6 months after publication of a rule finalizing the proposed warning statement requirements. To simplify the analysis, we assume that it would take all firms 6 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 of this document, 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.*

i. *Label Costs.*

(Comment 86) Some comments said that the proposed PDP or nonPDP 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, or about 6.6 square inches. The comment argued that the proposed warning statements cannot fit on a label of this size. One comment argued that the proposed warning statement would take up so much space on the label that firms would be able to provide very little other information on the label One comment argued that there is not enough room on package labels for multiple warning statements and suggested that we clarify that our proposed warning tatement would preempt any state labeling requirements.

(Response) We reviewed the labels of the 40 dietary supplements containing ephedrine alkaloids that we collected between March 20 and May 30, 2001, to investigate label size. Most labels were wrap-around adhesive labels with a minimum label size of about 7.5 square inches and an average of about 22.8 inches. Nearly all labels already bore extensive warning statements, and most of the content of the existing warning statements was distinct from the additional warning material required by some States. Therefore, we conclude that the proposed warning statements would probably have fit on most product labels. However, some dietary supplements containing ephedrine alkaloids, possibly including traditional style extracts, might have significantly smaller labels than the products that we collected. If we had adopted this option, we would have addressed this possibility in a number of ways. Firms that cannot fit the proposed PDP warning statement on the PDP if they use the normal font size would be able to use a smaller font size. Firms that cannot fit the nonPDP warning statement on the product labels could place the warning statement on any product labeling that is an integral part of the outer product packaging such that consumers may read the warning statement at the point of purchase, including the rise backing, panel extension, and oursert. In some cases, firms may already use these packaging features. These firms would simply need to revise the content of existing labeling. In other cases, firms might need to change the style of their packaging to utilize these types of labels. Rather than changing the style of their packaging, firms could also change the size of the package to increase the label space available for the warning statement. Changing the product packaging in one of these ways might require some firms to purchase new packaging machinery, which would be an additional cost beyond the cost of the label

changes that we discussed in the analysis of the June 1997 proposal. We have insufficient information to estimate the number of products that might need to take these steps. Based on our review of existing product labels, we estimate that the number of such products is probably very small.

We have reestimated labeling costs because we have new information on the number of dietary supplements containing ephedrine alkaloids and we have updated the labeling cost model that we used to estimate labeling costs in the analysis of the June 1997 proposed rule. The cost of changing labels varies with the amount of time that we give firms to change the labels. We previously proposed setting the effective date for this option to be 180 days after the publication of the final rule. According to the revised label cost model, the one-time cost of adding or revising a PDP and a nonPDP warning statement to the labels of all dietary supplements under a 6-month compliance period would be approximately $140 million to $319 million. The labeling cost model does not differentiate dietary supplements that contain ephedrine alkaloids from other dietary supplements. However, a database of dietary supplements compiled by Research Triangle Institute (RTI) under contract to FDA listed a total of 3,000 dietary supplement products in 1999, and 49 of those products, or about 2 percent, listed ephedrine or one of the following sources of ephedrine alkaloids in their ingredient lists: Ephedra, ephedra extract, ephedra herb, *Ephedra sinica* Stapf., ma huang, ma huang extract, ma huang herb, ma huang concentrate, or ma huang herb extract (Ref. 159). In the absence of other information, we assume that the cost of changing the labels of these products would be about 2 percent of the cost of changing all dietary supplement product labels. Therefore, we estimate that the one-time cost of changing the labels of dietary supplements containing ephedrine

alkaloids is $3 million to $6 million. Annualizing this cost over 20 years at 3 percent gives an annual cost that rounds to $0 million per year; that is, less than $500,000 per year. Annualizing this cost over 20 years at 7 percent gives an annual cost of $0 million to $1 million.

ii. *Risks of substitutes/absence of weight loss.*

(Comment 87) One comment noted that the proposed warning statement would instruct consumers not to take dietary supplements containing ephedrine alkaloids before or during strenuous exercise. This comment argued that this element of the warning statement could harm consumers by inhibiting weight loss because exercise is an essential component of a weight loss program.

(Response) As we discussed under Option Two of this section, we have insufficient information to estimate countervailing health effects such as the health risks generated by the use of substitute products or by the reduction or elimination of weight loss benefits. However, for this option, we have calculated benefits as a range of $0 to $20 million. This range is consistent with the existence of countervailing health risks from the source suggested by this comment.

d. *Effective date.*

(Comment 88) Some comments recommended that we revise the proposed effective date for the warning statement that we proposed in 1997 and revised in 2003. One comment suggested that we set the effective date to 12 months after publication of the final rule, rather than the proposed 180 days after publication of the final rule, to give industry more time to comply with the labeling requirements. Another comment suggested that we set the effective date to 60 days after publication of the final rule. Some comments suggested

that we base the effective date on labeling at the manufacturing site. Under this approach, we would require products leaving the manufacturing site after the effective date to bear the warning statements, but firms could continue to sell existing inventory without the warning statement after that date.

(Response) Setting the effective date to 12 months after publication of a final rule requiring the warning statement would lead to one time labeling costs of between $2 million and $5 million. Annualizing this cost over 20 years at 3 percent and 7 percent gives an annual cost that rounds to $0 million per year (i.e., less than $500,000 per year). This would also reduce benefits in the first year to $0 under the simplifying assumption that all firms would take 12 months to comply with the required warning statement.

Eliminating all costs associated with unusable label or package inventory by allowing firms to continue to sell product without the warning statement after the effective date would lead to compliance costs of $2 million to $6 million under the proposed 180 day compliance period. Annualizing this cost over 20 years at 3 percent gives an annual cost that rounds to $0 million per year (i.e., less than $500,000 per year). Annualizing this cost over 20 years at 7 percent gives an annual cost of $0 million to $1 million per year. In our summary statements, we present the cost estimates under the 7 percent discount rate because that range includes the range of costs that we estimated under a 3 percent discount rate. However, this option would also generate additional enforcement costs because we would need some way of determining that the products that firms sell without the warning statement were actually labeled before the effective date. In addition, this revision would reduce benefits over a number of years according to the proportion of products sold during that time that did not bear warning statements. The period over which

benefits would be reduced could be quite large because firms might produce as much product as possible prior to the effective date to avoid having to meet the labeling requirements. The comments did not provide information on this issue, and we are unable to estimate this reduction in benefits.

We compare costs of different effective dates for the proposed labeling option in table 7 of this document. We only consider first year net benefits because changing the effective date from 180 days to 365 days only affects benefits in the first year. After the first year, annual benefits would be the same for either effective date. To obtain the higher bound estimate of net benefits, we start with the higher bound estimate of benefits and subtract the lower bound estimates of costs. To obtain the lower bound estimate of net benefits, we start with the lower bound estimate of costs and subtract the higher bound estimate of costs. We do not have information suggesting that any of these options would lead to greater net benefits than the proposed enforcement period of 180 days.

TABLE 7.—COMPARISON OF EFFECTIVE DATE OPTIONS FOR OPTION THREE (REQUIRE THE PROPOSED WARNING STATEMENT), ROUNDED TO $ MILLIONS

Effective Date	Annualized Cost (millions)	First Year Benefits (millions)	First Year Net Benefits (millions)
180 days	$0 to $1	$0 to $10	-$1 to $10
365 days	$0	$0	$0
180 days at manufacturing site	$0 plus additional enforcement costs	NA	NA

e. *Conclusions on the benefits and costs of 2003 proposed warning statement.* We estimate costs to include the one-time cost of changing the 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 in section VIII.A.5 of this document. 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.*

(Comment 89) Some comments addressed the placement of the proposed warning statement on product packages. Some comments suggested that we allow firms to use inserts, stickers, or "peel away" labels. One comment said that we should allow firms to use alternative methods of disseminating warning information if they dispense products that are part of a bulk decoction

formula that lacks standard labeling, such as products compounded and dispensed in Chinese herbal medicine pharmacies or by "qualified health professionals."

(Response) According to the March 2003 notice, we proposed to allow firms to use special labeling for the nonPDP warning statement as long as consumers could read the warning statement at the point of purchase.

(Comment 90) Some comments objected to the PDP warning statement that was part of the revised warning statement that we proposed in 2003. Other comments supported the 2003 proposed PDP warning statement. Some comments suggested that we require firms to use the PDP warning statement on both the product container and the outside container or wrapper of the retail package. One comment suggested that we require firms to include the PDP warning statement in any promotional literature and advertising.

(Response) Eliminating the PDP warning statement but retaining the nonPDP warning statement would probably significantly reduce the impact of the proposed warning statement. The PDP warning statement was one of the main elements of the proposed warning statement that differed from most existing warning statements. Reducing the impact of the warning statement by eliminating the proposed PDP warning statement would reduce both the benefits and the distributive impacts of the warning label option. However, eliminating the PDP warning statement would have little impact on the overall cost of changing labels to comply with the proposed warning statement because firms would still need to change labels even if we did not require a PDP warning statement. Requiring firms to place the warning statement on both the product container and the outside container or wrapper and requiring firms to include it in any promotional literature and advertising might increase

the impact of the warning statement, but would also increase the costs. The comments did not provide sufficient information to establish that the benefits from these revisions would outweigh the costs.

(Comment 91) One comment argued that the PDP for mail order dietary supplements corresponds to the front page of any product literature that a firm uses to advertise its product. This comment said that the proposed regulation would, therefore, require some firms to change their pamphlets and other material. The comment argued that such a requirement would put mail order businesses at a competitive disadvantage relative to retail businesses. The comment suggested that we allow the warning statement to appear either above the mail order form that consumers use to order the product or above the toll free telephone number that consumers call to order the product. The comment argued that these locations would be more similar to the labeling requirements for OTC drugs.

(Response) The PDP for mail order dietary supplements is defined in the same way as the PDP for supplements sold in other ways: The label that appears on the front of the product package. It does not correspond to the front page of any product literature that a firm uses to advertise its product.

(Comment 92) Some comments objected to the requirement that firms set off the warning statement in a box graphic. One comment argued that the 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 shortening the proposed PDP warning statement would make it more effective. One comment noted that the proposed approach is inconsistent with the "signal/refer/explain" format used for the labeling of other hazardous products. However, one comment suggested that we add material to the PDP warning statement, rather than shortening it.

(Response) Revising the PDP warning statement for some or all dietary supplements that contain ephedrine alkaloids would have little effect on labeling costs because firms would still need to revise their labels even if we did not require a PDP warning statement. The comments did not provide sufficient information to establish that revising the PDP warning statement would increase net benefits.

(Comment 94) A number of comments raised the issue of whom we instruct consumers to contact under various conditions. The proposed PDP and nonPDP warning statements suggest that consumers contact a "doctor" under various conditions. Some comments suggested we use a more general phrase such as "health care provider" in order to include nurse practitioners and pharmacists. One comment suggested that we change "doctor" to "licensed health care provider" to include acupuncturists who are trained in traditional Chinese medicine. The comment noted that at least half of the states that regulate the practice of acupuncture include the use of herbs in the authorized scope of practice of acupuncturists. The comment also noted that herbal ephedra is used by health care providers in other disciplines, such as naturopathy and herbalism. This comment argued that it was important to protect the ability of these groups to dispense dietary supplements containing ephedrine alkaloids.

(Response) Changing the specification of the person that the proposed warning label directs consumers to contact under various conditions would have little impact on labeling costs but would affect the benefits and distributional effects of this rule. Medical doctors are probably in the best position to advise consumers on the health implications of consuming ephedrine alkaloids under various conditions, but consumers might be able

to get comparable advice from some other sources, including pharmacists and other health care providers, as well as some practitioners of acupuncture, herbalism, and naturopathy. On the other hand, obtaining advice from a medical doctor is probably more costly for many consumers than obtaining advice from other potential sources. In addition, some consumers may be unwilling to seek advice from medical doctors on the use of dietary supplements for reasons other than cost. These consumers may be less likely to follow directions to contact a medical doctor than they are to follow directions to contact a broader variety of health care providers. This component of the warning statement could also have distributional effects because directing consumers to contact a medical doctor increases the demand for the services of medical doctors and reduces the demand for the services of competing health care providers. The comments did not provide sufficient information to allow us to determine that changing the specification of the person that the label directs consumers to contact would increase net benefits. The comments also did not provide enough information for us to quantify the potential distributional impact of revising this component of the label.

(Comment 95) Some comments noted that the PDP warning statement implied that ephedrine alkaloids cause heart attack, stroke, seizure, and death. These comments argued that this is misleading because no one has proven 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 nonPDP warning statement.*

(Comment 96) A number of comments suggested that we revise the proposed nonPDP warning statement. Some comments suggested that we use the same warning statement that appears on OTC drug products containing ephedrine alkaloids. One comment suggested that we allow firms to use the OTC warning statement for dietary supplements that they sell directly to health professionals for subsequent sale to consumers. One comment argued that the warning statement should not instruct consumers to contact a doctor if they

experience nausea because nausea is not likely to be a precursor symptom of a potentially serious or life-threatening condition.

Some comments objected to the warning that the risk of serious side effects increases with duration of use. One comment suggested that the scientific data showed that adverse effects dramatically decline with continued use. Some comments argued that there was no persuasive evidence that ephedrine alkaloids had any cumulative effect on the cardiovascular or central nervous systems.

One comment suggested that we allow manufacturers to add contraindications beyond those listed on the required warning label. One comment suggested that we require a statement clarifying that we have not reviewed the product for safety or efficacy. Some comments argued that we should require warning statements to include the toll free telephone number and Web site address for our MedWatch program. Some comments recommended that we require firms to indicate the amount of ephedrine alkaloids present in a product on the product label.

(Response) These comments did not provide sufficient information to analyze the costs and benefits of revising the proposed nonPDP warning statement according to their recommendation.

e. *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.

8. Option Five—Generate Additional Information or Take Some 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 risks associated with ephedrine alkaloids (Ref. 34). One comment noted that the NIH National Advisory Council for Complementary and Alternative Medicine Working Group on *Ephedra* suggested that someone perform a multi-site prospective case-control study to assess the risks associated with taking ephedra. This comment suggested that such a study would require 4 to 8 years to complete and cost $2 million to $4 million per year. Anotner comment argued that even if someone were to establish that ephedrine alkaloids increased cardiovascular risk by raising blood pressure, someone would still

need to do a controlled research study to determine whether that effect outweighed the reduction in cardiovascular risk resulting from any weight loss generated by these products. One comment argued that a retrospective case control study is the correct study design for rare events. This comment argued that someone could do multiple studies of this type because they are quick, relatively inexpensive, and because the population exposure level is relatively high at 1 percent, according to a multistate survey on reported use of ephedra products from 1996 to 1998. Some comments suggested that we not take regulatory action until we determine that the adverse events that we suspect are caused by these supplements are due to ephedrine alkaloids rather than due to inconsistent and inaccurate formulations.

Some comments argued that we do not need to generate additional information because we already have sufficient information to remove dietary supplements containing ephedrine alkaloids from the market or require warning statements. Other comments argued that we do not need to generate additional information because we already have sufficient information to establish that these restrictions are unnecessary. Some of these comments argued that Morgenstern et al., which was published after the RAND report, was just the type of case control study that the RAND report recommended (Ref. 136). These comments noted that this study found that ephedra did not raise the risk for hemorrhagic stroke. However, other comments argued that this study found that ephedra did raise the risk for hemorrhagic stroke. Some comments criticized various aspects of that study. A number of comments argued that the only additional studies that would be worthwhile to perform at this point would be unethical. These comments suggested that a human subjects committee would not allow a prospective study of the safety of

ephedrine alkaloids without medical screening. They also suggested that a cohort study would be difficult because ephedrine alkaloids do not generate significant health benefits and also because of the ethical requirements to effectively inform participants of the risks.

(Response) Generating additional information might reduce the remaining uncertainty associated with the benefits of this rule or it might not. Generating additional information may be difficult, time consuming, and expensive. In addition, it is not clear that reducing the remaining uncertainty would change the outcome of this rulemaking. The comments did not provide sufficient information to allow us to estimate the costs and benefits of delaying rulemaking until we generate additional information.

(Comment 98) Other comments suggested that we should take some type of action other than issuing a regulation or generating additional information. A number of comments suggested that we address any problems with dietary supplements containing ephedrine alkaloids by using our existing authority to seize unsafe or adulterated dietary supplements. Other comments suggested that we address any problems by using our existing authority to investigate and prosecute unscrupulous multilevel marketing (MLM) 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 issuing 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.

9. 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 includes alternative assumptions about the value of a statistical life ($5 million and $6.5 million) and the value of a statistical life year ($0.1 million, $0.3 million, and $0.5 million). We also considered a reporting rate of 50 percent, which leads to estimated annual benefits of $9 million to $26 million, and 100 percent, which leads to estimated annual benefits of $4 million to $13 million. More precise estimates of the health benefits would depend on choosing a particular combination of assumptions.

Removing these products from the market will generate one-time product reformulation costs of $10 million to $100 million, which amounts to a yearly cost of $1 million to $7 million when annualized over 20 years at an interest rate of 3 percent, and $1 million to $9 million at an interest rate of seven percent. These costs could be partly offset by reductions in fees associated with legal actions involving these products. In addition to the social costs, removing dietary supplements containing ephedrine alkaloids from the market could also generate distributional effects under which some firms manufacturing or distributing dietary supplements containing ephedrine alkaloids may experience reduced profits, while firms manufacturing or distributing other dietary supplements or other weight loss alternatives may experience increased profits. In addition, removing dietary supplements containing ephedrine alkaloids from the market would also generate costs in the form of lost consumer utility or satisfaction because of the removal of a product from the market. We estimated lost utility to be $6 million to $81 million per year.

Based on these estimates, the potential economic effects of this rule range from a net annual social cost of $90 million per year, if the rule's net health benefits are zero because of countervailing health effects or because consumers already understand and voluntarily accept the risks posed be 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

TABLE 8.—SUMMARY OF OPTIONS, ROUNDED TO $ MILLIONS--Continued

Option	Annual Cost	Annual Benefit	Net
3 Require 2003 warning statement	$0 to $1	$0 to $20	- $1 to $20
Require warning statement, but modify it or require only on certain products	NA	NA	NA
5 Generate additional information 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) and in accordance with Executive Order 13272 (August 13, 2002). If 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 proposed rule. This database listed 30 firms associated with 48 dietary supplement products containing ephedrine alkaloids (Ref. 159). To estimate the number of these firms that are small, we used a database of dietary supplement manufacturing practices that was also compiled by RTI under

contract to FDA (Ref. 160). This database had size information for only a few of the 30 firms that we identified as relevant from the first database. Therefore, we estimated the number of small firms based on the percentage of all dietary supplement firms in the database that would qualify as small firms. The Small Business Administration (SBA) publishes definitions of small businesses by the North American Industry Classification System (NAICS) code. The firms in the database fell into the following NAICS codes: (1) 311222 Soybean Processing, (2) 311920 Coffee and Tea Manufacturing, (3) 325188 All Other Basic Inorganic Chemical Manufacturing, (4) 325199 All Other Basic Organic Chemical Manufacturing, (5) 325411 Medicinal and Botanical Manufacturing, and (6) 325412 Pharmaceutical Preparation Manufacturing. SBA defines small businesses in these NAICS codes based on a maximum number of employees, as follows: 311222 and 311920—no more than 500 employees; 325411 and 325412—no more than 750 employees; and 325188 and 325199—no more than 1000 employees. The database of firms listed 1,566 individual plants and 146 parent companies. Essentially all individual plants qualified as small businesses (98 percent under a maximum of 500 employees and 100 percent under a maximum of 1,000 employees). However, approximately 12 percent of the individual plants were associated with parent companies, and only about half of the parent companies qualified as small businesses (53 percent under a maximum of 500 employees and 58 percent under a maximum of 1,000 employees). Based on this information, we estimated that about 94 percent of the 30 firms associated with dietary supplement containing ephedrine alkaloids, or about 28 firms, would qualify as small businesses.

There may also be a number of independent distributors that are not captured in our database of dietary supplement firms. All or most of these

firms would probably qualify as small businesses. However, we do not have sufficient information to estimate the number of distributors or to compare their characteristics to the SBA definition of a small business for that industry. As we noted in the previous paragraphs, this final rule will generate shifts in demand that might adversely affect these firms. However, the most likely substitutes for dietary supplements containing ephedrine alkaloids are other dietary supplements, and the same distributors that handle dietary supplements containing ephedrine alkaloids might also handle these other dietary supplements. Therefore, the net distributive impact on small distributors may be small or nonexistent. Although demand shifts generated by this final rule might also increase business for other small businesses, we do not consider countervailing positive effects on other small entities when assessing the impact of our rules on small entities.

In response to the request that we open a dialogue with industry associations, we note that small entities, and trade associations (with member small entities) submitted a number of comments regarding small business impact during the various comment periods for this rulemaking.

In the preceding cost-benefit analysis, we estimated that removing dietary supplements containing ephedrine alkaloids from the market would generate annualized cost of $1 million to $9 million over 20 years because of the need to reformulate products. This would correspond to a cost per firm across 30 firms of between $30,000 and $300,000 per year. In addition, we estimated that profits might be reduced by $0 to $13 million per year due to decreased sales. Profits may accrue to either manufacturers or distributors. If all profit losses affected manufacturers only, then the annual profit loss per firm across 30 firms would be between $0 and $ 430,000, which would give a total cost

per firm of $30,000 to $730,000. Most of these firms are small, so even $30,000 per year (the lower bound) would be a significant additional burden. We previously estimated total sales to be $559 million to $806 million. If we assume that profits correspond to approximately 5 percent of sales, then annual profits would be $28 million to $40 million. If we assume that all profits accrue to manufacturers, then profits would be $0.9 million to $1.3 million per year per firm across 30 firms. In that case, reformulation costs would represent 2 percent to 33 percent of total profits, while total costs would represent 2 percent to 81 percent of total profits. The Regulatory Flexibility Act does not specify a threshold for costs to have a significant economic impact, but the 2 ranges we have calculated reach a high fraction of total profit; for some individual small firms the fraction of profit would be higher. If some of the profit losses accrued to distributors rather than manufacturers, then the potential cost per firm across all firms would be lower. However, we have insufficient information to estimate the number of distributors or the sales or profits per distributor.

(Comment 100) One comment argued that the PDP warning statement would have a significant economic impact on small businesses. This comment argued that the nonPDP warning statement would be adequate to protect consumers. This comment recommended that we eliminate the PDP warning statement.

(Response) A PDP warning statement might have a significant impact on small businesses. We have analyzed the costs of the proposed warning statement as a whole (including both PDP and nonPDP components) in our analysis of impacts under Executive Order 12866. However, the comment did not provide sufficient information to differentiate the impact on small

businesses from the impact on other regulated entities, or to differentiate the impact of the PDP warning from the impact of the nonPDP warning.

(Comment 101) One comment recommended that we consider reasonable alternatives to the rule in order to reduce the burden on small businesses

(Response) The discussion of regulatory options in the preceding benefit-cost analysis pertains primarily to small businesses because nearly all affected firms are small businesses under SBA size definitions. We could develop a definition of a very small business (different from the SBA definition of a small business) and develop additional regulatory options to reduce the burden on those firms, but those options would also be similar to those in the benefit-cost analysis. As we stated elsewhere in this analysis, any option that would reduce the regulatory burden on very small firms would also reduce benefits by increasing the risk to public health. We do not have sufficient information to compare the value of the regulatory relief for very small firms to the associated reduction in benefits.

IX. Environmental Impact

Removing dietary supplements containing ephedrine alkaloids from the market will not have a significant impact on the human environment. Therefore, an environmental impact statement is not required.

X. Paperwork Reduction Act

This final rule contains no collections of information. Therefore, clearance by OMB under the Paperwork Reduction Act of 1995 is not required.

XI. Federalism

We have analyzed this final rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the rule has a preemptive effect on State law. Section 4(a) of the Executive order requires agencies to "construe * * * a Federal statute to preempt State law only

where the statute contains an express preemption provision or there is some other clear evidence that the Congress intended preemption of State law, or where the exercise of State authority conflicts with the exercise of Federal authority under the Federal statute." Section 402(f)(1)(A) of the act states that a dietary supplement or dietary ingredient shall be considered adulterated if it presents a significant or unreasonable risk of illness or injury under conditions of use recommended or suggested in the product's labeling. If no conditions of use are suggested or recommended in the product's labeling, the dietary supplement or dietary ingredient is considered to be adulterated if it presents a significant or unreasonable risk of illness or injury under ordinary conditions of use. We have concluded that dietary supplements containing ephedrine alkaloids present an unreasonable risk and are therefore adulterated under section 402(f)(1)(A) of the act.

Section 402(f)(1)(A) of the act does not expressly preempt State or local laws. Therefore, under section 4(b) of Executive Order 13132, we are to construe our rulemaking authority as authorizing preemption of State law by rulemaking "only when the exercise of State authority directly conflicts with the exercise of Federal authority under the Federal statute or there is clear evidence to conclude that Congress intended the agency to have the authority to preempt State law."

We are aware that several States have laws concerning dietary supplements containing ephedrine alkaloids, such as required label statements, which clearly contemplate the continued marketing of such products. Section 301(a) of the act (in relevant part) prohibits the introduction or delivery for introduction into interstate commerce of any adulterated food. In this rule, the agency has declared dietary supplements containing ephedrine alkaloids to be

adulterated. As a result, State laws establishing label requirements or other requirements that contemplate the continued marketing of these products conflict with this final rule and, consequently, are preempted.

Section 4(c) of Executive Order 13132 instructs us to restrict any Federal preemption of State law to the "minimum level necessary to achieve the objectives of the statute pursuant to which the regulations are promulgated." This action meets the preceding requirement because it only applies to State laws that contemplate the continued marketing of this class of products.

Section 4(d) of Executive Order 13132 states that when an agency foresees the possibility of a conflict between State law and federally protected interests within the agency's area of regulatory responsibility, the agency "shall consult, to the extent practicable, with appropriate State and local officials in an effort to avoid such a conflict." Section 4(e) of Executive Order 13132 adds that, hen an agency proposes to act through adjudication or rulemaking to preempt State law, the agency "shall provide all affected State and local officials notice and an opportunity for appropriate participation in the proceedings."

In the present rulemaking, consultation with and notice to State officials under section 4(d) and (e) of Executive Order 13132 did not occur before we published the June 1997 proposal. Such consultation and notice was not possible because we published the proposed rule in the **Federal Register** of June 4, 1997, and Executive Order 13132 was not signed until August 4, 1999. OMB's guidance for implementing Executive Order 13132 states that, when a final rule may have been issued as a proposed rule before August 4, 1999, such that the intergovernmental consultation process had not occurred as called for by Executive Order 13132, the agency's certification "should so state" (see Memorandum for Heads of Executive Departments and Agencies,

and Independent Regulatory Agencies, dated October 28, 1999) (Ref. 181). Thus, we certify that the intergovernmental consultation process described in Section 4(d) of Executive Order 13132 did not occur for the proposed rule, but we also believe that State and local governments had sufficient notice and an opportunity to participate in this rulemaking process. We note that the proposed rule was subject to a previous Executive Order, Executive Order 12612, which was also entitled, "Federalism," and had a similar consultation and notification obligation for federal agencies. When we issued the proposed rule, we notified the States, and State and local health departments, among others, submitted comments to the proposal (65 FR 17474, April 3, 2000) (stating that State and local health departments and government agencies had commented on the proposed rule)). Furthermore, a subsequent notice, published on March 5, 2003, expressly asked whether we should determine that dietary supplements containing ephedrine alkaloids present a "significant or unreasonable risk of illness or injury" under section 402(f)(1)(A) of the act (68 FR at 10417, 10419, and 10420). Although the March 2003 notice did not contain a separate Federalism analysis, we believe that States were aware of the March 2003 notice because at least five State or local governments or legislators submitted comments in response to the March 2003 notice, and most of these comments urged us to ban the sale of such products.

XII. References

The following references have been placed on display in the Division of Dockets Management (see **ADDRESSES**) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday. (FDA has verified the Web site addresses, but FDA is not responsible for any subsequent changes to the nonFDA Web sites after this document publishes in the **Federal Register**.)

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2. Chen, K. K. and C. F. Schmidt, "Ephedrine and Related Substances," *Medicine* vol. 9, pp. 1–117, 1930.

3. Mahuang (Appendix: Mahuanggen)., Chapter in Chang, H-M. and P. P-H. But, eds., *Pharmacology and Applications of Chinese Materia Medica*, pp. 1119–1124, Singapore: World Scientific Publishing Co. Pte. Ltd., pp. 1119–1124. 1987.

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List of Subjects in 21 CFR Part 119

Dietary ingredients, Dietary supplements, Foods.

■ Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 119 is added as follows:

■ 1. Part 119 consisting of § 119.1 is added to read as follows:

PART 119—DIETARY SUPPLEMENTS THAT PRESENT A SIGNIFICANT OR UNREASONABLE RISK

§ 119.1 Dietary supplements containing ephedrine alkaloids.

Dietary supplements containing ephedrine alkaloids present an unreasonable risk of illness or injury under conditions of use recommended or suggested in the labeling, or if no conditions of use are recommended or

suggested in the labeling, under ordinary conditions of use. Therefore, dietary supplements containing ephedrine alkaloids are adulterated under section 402(f)(1)(A) of the Federal Food, Drug, and Cosmetic Act.

Authority: 21 U.S.C. 321, 342, 343, 371.

Dated: January 28, 2004

Mark B. McClellan,
Commissioner of Food and Drugs.

Dated: FEB 4 2004

Tommy G. Thompson,
Secretary of Health and Human Services.

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