XXIV. Analysis of Impacts

A. Introduction

FDA has examined the economic implications of this final rule as required by Executive Order 12866. Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). Executive Order 12866 classifies a rule as significant if it meets any one of a number of specified conditions, including: Having an annual effect on the economy of $100 million, adversely affecting a sector of the economy in a material way, adversely affecting competition, or adversely affecting jobs. A regulation is also considered a significant regulatory action if it raises novel legal or policy issues. FDA has determined that this final rule will be an economically significant regulation under Executive Order 12866 because it will have an annual effect on the economy of more than $100 million.

The Small Business Regulatory Enforcement Fairness Act of 1996 (Public Law 104-121) defines a major rule for the purpose of congressional review as being likely to cause one or more of the following: An annual effect on the economy of $100 million; a major increase in costs or prices; significant adverse effects on competition, employment, productivity, or innovation; or significant adverse effects on the ability of United States-based enterprises to compete with foreign-based enterprises in domestic or export markets. In accordance with the Small Business Regulatory Enforcement Fairness Act, OMB has determined that this final rule will be a major rule for the purpose of congressional review.

FDA has examined the economic implications of this final rule as required by the Regulatory Flexibility Act (5 U.S.C. 601- 612). If a rule has a significant economic impact on a substantial number of small entities, the Regulatory Flexibility Act requires agencies to analyze regulatory options that would lessen the economic effect of the rule on small entities. FDA finds that this final rule will have a significant economic impact on a substantial number of small entities.

The Unfunded Mandates Reform Act of 1995 (Public Law 104-4) requires cost-benefit and other analyses for rules that would cost more than $100 million in a single year. The current inflation-adjusted statutory threshold is $115 million. This final rule qualifies as a significant rule under the statute.

1. Summary of the Economic Analysis

We carry out the cost-benefit analyses required for significant rules in the Final Regulatory Impact Analysis, in section XXIV.B of this document. We perform the Final Regulatory Flexibility Analysis of the effects on the final rule on small businesses in section XXIV.C of this document. We estimate that, once it is fully implemented 36 months after the date of publication, the quantifiable annual benefits from the final rule will be about $48 million. The quantified benefits are generated by more consistently produced dietary supplements which will increase product safety, which reduces the number of acute illnesses and product recalls. In addition, the final rule will generate benefits that we lack sufficient data to quantify. These benefits we cannot quantify arise from dietary supplements manufactured under a system to ensure quality, which

leads to a reduction in the number of chronic illnesses and conditions.

The final rule will lead to quantifiable costs of $9 million in the first year it takes effect, $136 million in the second year, and $167 million in the third year. After 3 years the annual costs will be about $150 million. If we annualize the benefits and costs over 20 years at a 3 percent rate of discount, the annualized quantifiable benefits are $44 million and annualized quantifiable costs are $140 million. These annualized benefits include only those that we are able to quantify. The total annualized benefits will be larger than our estimate of $44 million in quantifiable benefits because of the benefits that we are not able to quantify.

We have determined, based on information contained in this regulatory impact analysis as well as information contained elsewhere in the preamble, that the benefits of this final rule justify the costs. We believe that dietary supplements are purchased based on product labels or labeling. If consumers believe that most dietary supplements are expected to contain the ingredients as labeled, as with any other product they purchase, then we should help to ensure that they are

manufactured under a system to ensure quality, including the proper identity, amount of ingredients and limits on contaminants. We have determined that, , the costs of ensuring the quality of dietary supplements are justified by the benefits including those that are related to increased safety.

The final rule will have a significant economic effect on small businesses. We estimate that the annual costs will be about $41,000 for an establishment with fewer than 20 employees and $163,000 for an establishment with 20 to 499 employees.

2. Summary of Comments on the Economic Analysis

We received numerous substantive comments on the economic analysis of the 2003 CGMP Proposal. In general, comments from the dietary supplement industry state that we underestimated the cost of the 2003 CGMP Proposal. Specific comments from the industry target the 2003 CGMP Proposal's testing requirements, which the comments characterize as "burdensome." Many comments address our estimate of the number of batches of dietary supplements firms produce in a year. Many comments express the fear that, as a result of this 2003 CGMP Proposal, the prices consumers pay for dietary supplements would increase

dramatically. Nearly all economic comments mention potential adverse effects of the 2003 CGMP Proposal on small businesses, stating that many firms would have to stop manufacturing. A few comments state that, if made final, the 2003 CGMP Proposal would make dietary supplements more expensive than pharmaceuticals. Other comments address the following topics:

- FDA's other assumptions, including the number of tests required for each batch and the number of tests already being performed.
- Development of analytical methods.
- Equipment and capital investment costs.
- Recordkeeping costs.
- Number of batches produced per year.
- FDA's estimation of benefits.

We will summarize comments on individual substantive issues under the appropriate subject headings and respond.

B. Final Regulatory Impact Analysis

1. The Need for the Final Current Good Manufacturing Practice Rule

The final rule is needed because establishments that manufacture, package, label, or hold dietary supplements may not have sufficient market incentives to use controls to ensure that the quality of the supplements is what consumers would choose to buy if they had adequate information on product quality. As a result there may be adulteration of dietary supplements relating to, among other things, their identity, purity, strength, and composition. Manufacturing, packaging, labeling, and holding practices that ensure quality can be costly and problems can be undetectable by consumers, so establishments may not adopt them unless required to do so by regulation. Actions by manufacturers, primarily voluntary quality controls, do not provide sufficiently protective industry-wide minimum requirements for manufacturing, packaging, labeling, or holding of dietary supplements. Some firms subscribe to fee-for-service quality control programs, but these programs do not regularly inspect the facilities to ensure that they are meeting the program's standards. Without the final rule, products in the dietary supplement market are likely to be sorted into two types:

- Higher-priced products with respected brand names or industry certification that follow several of the CGMP requirements found in this final rule;
- Lower-priced products that contain no private certification or respected brand name and that follow few of the CGMP requirements found in this final rule.

In today's market for dietary supplements, to find information on the properties of products consumers must sort through information from the Internet, magazines, brochures, popular books, television, and a host of other sources. The information from these sources deals most often with the claims for the products themselves, not with the steps taken by establishments to limit contamination or to ensure quality. The inadequate information on manufacturing practices makes this final rule necessary to ensure the quality of dietary supplements.

(Comment 337) We received several comments on the need for the 2003 CGMP Proposal. Four comments specifically support the proposal, stating in part that they are pleased we are addressing the issue of dietary supplement manufacturing. In addition, one comment states that the 2003 CGMP Proposal was a

good step toward providing assurance that dietary supplements are as safe as prescription and OTC drugs.

Other comments express concern about the 2003 CGMP Proposal. One comment generally supports it but expresses concern that the statements we make regarding market incentives to prevent adulteration and misbranding are inaccurate and misleading. The comment points out that the incentive exists for firms to prevent adulterated products from entering the marketplace because of their desire to avoid damage to their reputations. In addition, adulterated products are already illegal to market. Two other comments support the 2003 CGMP Proposal only with modifications, and another comment supports current good manufacturing practice regulations, provided they reflect the current "best practices of leading manufacturers." Two comments assert that a "more rigorous" enforcement program would be more effective than dietary supplement CGMP requirements in preventing adulteration. Two comments state that a regulation would serve no useful purpose because of the "low level of harm identified in the industry."

One comment states that the 2003 CGMP Proposal spells out design standards rather than performance standards. According

to the comment, the 2003 CGMP Proposal spells out procedures a firm must follow rather than defining a specific outcome, such as a specified level of contamination. This comment maintains that we should set a performance standard and then allow manufacturers flexibility in how that standard is reached. Another comment states that, although certain dietary supplement ingredients may cause concern, this concern did not justify imposing "overbearing" and "broad" CGMP regulations for an entire industry. Another comment asserts that the CGMPs as presented in the 2003 CGMP Proposal would serve as an anti-competitive tool by allowing dominant manufacturers to increase their dominance and make it more difficult for new firms to enter the industry.

(Response) These comments failed to provide evidence that the final rule is not needed. We agree with the comments that point out that existing statutes and regulations, concern for brand names, and voluntary industry standards can provide some product safety and quality. Nonetheless, continuing problems in the industry demonstrate the need for this final rule. For example, from 2000 to 2003, there were a total of 41 recall actions in the dietary supplement industry, covering class 1, 2,

and 3 recalls, of vitamins and minerals and herbal and botanical supplements. These recalls were all related to a failure of the company to adhere to product manufacturing or labeling specifications. For a class 1 recall, there is a reasonable probability of serious adverse health consequences or death; for a class 2 recall, exposure to the product may cause temporary or medically reversible adverse health consequences; for a class 3 recall, exposure to the product is not likely to cause adverse health consequences. Full compliance with the provisions of this final rule could have prevented all those recalls. The continued problems with the safety and quality of dietary supplements show the need for the additional protection provided by this final rule. The results from ConsumerLab.com, other independent laboratory results, and continued problems with contaminated supplements provide further evidence of a need for this final rule (Refs. E26-E29). Although this evidence is helpful, there may also be data on adverse events known only to the supplement manufacturers.

2. Regulatory Options

We considered several regulatory options for dealing with current manufacturing, packaging, labeling, and holding

practices that may not ensure the quality of the dietary supplement. The options considered include: (1) No new regulatory action, (2) fewer requirements for vitamins and minerals, (3) more restrictive regulations than the final rule, (4) HACCP without the other elements of the final rule, (5) final product testing only, (6) a final rule for high-risk products or hazards only, and (7) the 2003 CGMP Proposal. As a result of comments on the 2003 CGMP Proposal and our reconsideration of our position on several provisions, this final rule differs from the 2003 CGMP Proposal.

(Comment 338) We received few comments on the option of fewer requirements for vitamins and minerals, and the comments submitted did not support this option. One comment supports one set of CGMPs that would apply to the entire industry rather than fewer requirements for vitamins and minerals than for botanicals. Another comment states that having fewer requirements for vitamins and minerals would not be wise because of the large number of people who take multivitamin or mineral supplements.

One comment supports more restrictive CGMP requirements, including further testing and quality assurance requirements.

We received two comments that support HACCP without other elements of the final rule. One comment echoes an earlier comment made about stressing outcomes and points to the HACCP systems in the juice and seafood industries as a way of ensuring effective quality control design. The comment asserts that the detailed manufacturing controls and testing requirements spelled out in the 2003 CGMP Proposal may actually stifle innovation. Another comment echoes these thoughts, adding that a HACCP approach could work in tandem with a more traditional specification and test approach.

We received one comment that specifically discusses requiring only final product testing, but received numerous comments on final product testing in general. The specific comment did not support reliance on final product testing only, stating it is not the best or most appropriate control. In addition, the comment claims it is not technically feasible in many cases and is economically burdensome, a point repeated in other general comments about final product testing. In addition, numerous comments point out that a firm cannot "test in quality," meaning that ensuring the quality of the dietary supplement will not be achieved through rigorous end-product

testing, which emphasizes the wrong stage of production, but by ensuring quality through an effective process control system.

Few comments discuss regulation of only high-risk products. Those that did note that some ingredients would be of public health concern and it would be preferable to test these ingredients only rather than all ingredients.

(Response) The comments on the regulatory options did not provide evidence to directly support or oppose those options but instead addressed particular issues such as testing or coverage.

We took the comments on specific issues into account in the analysis of this final rule. We discuss them below in the relevant parts of the analysis.

One comment supporting HACCP stated that the detailed manufacturing and testing requirements of the 2003 CGMP Proposal would, compared with HACCP, stifle innovation. Although regulations that impose costs will divert resources away from innovation, the diversion caused by the final rule will not be large enough to stifle innovation. As we explained in the economic analysis of the 2003 CGMP Proposal, the HACCP option would not specify detailed manufacturing requirements but would

also fail to ensure product quality (68 FR 12157 at 12222). The comment supporting HACCP did not provide any evidence that would lead us to change that conclusion.

3. Coverage of the Final Rule

The final rule applies to establishments that manufacture, package, label, or hold dietary supplements. Tables 20 and 21 list the estimated number of covered manufacturers, packagers, labelers, holders, and other establishments subject to the final rule. Table 20 shows the number of establishments categorized as manufacturers, re-packagers or re-labelers, holders whose primary business is dietary supplements, and other (although not including other holders and distributors). Table 21 shows our estimate of the number of general warehouses, wholesalers, and others that hold dietary supplements, but are not otherwise involved in the industry.

Table 20. Covered Establishments by Type of Operation from DS-EED

Establishment Type	Number of Establishments	Percent of Establishments
Manufacturer	1,228	84.1
Re-packager; re-labeler	26	1.8
Holder	114	7.8
Establishments not already classified	92	6.3

Total	1460	100.0

Table 21. Covered Establishments That Hold Dietary Supplements

Type of Holders	NAICS Code	Number of Establishments
General Grocery Wholesalers or Drug Wholesalers	424410	4,036
General Warehouse	493110	4,415
Drug Wholesalers	42420	7,418
Total		15,869

We consulted several sources to estimate the number of establishments reported in this document. The number, 1,460, is the estimated number of establishments in the Dietary Supplement Enhanced Establishment Database (DS-EED) that manufacture, package, label, or hold dietary supplement products in the United States. In the analysis of the 2003 CGMP Proposal, we included an additional 106 U.S. establishments that supplied dietary ingredients. Because those establishments are not covered in this final rule, we exclude them from the total. RTI developed the DS-EED using FDA's Official Establishment Inventory (OEI) and supplemented that source with information from trade organizations, trade shows, and electronic databases (Refs. E2 and E3).

To estimate the total number of establishments that could hold dietary supplements but do not consider dietary supplements as their primary business, we first looked for a count of establishments that had North American Industrial Classification System (NAICS) codes for wholesalers of groceries or drugs. Next we looked for a count of firms that met the description of warehouses for groceries or drugs. We did not find a category devoted exclusive to food and drug warehousing, so we concluded that general warehousing most closely corresponded to the set of establishments that would hold dietary supplements. The results are shown in table 21. This total differs from the total reported in the analysis of the 2003 CGMP Proposal because the new classification system allows us to identify more establishments that would not hold dietary supplements and therefore exclude them from the total.

Foreign firms that export dietary supplements to the United States must satisfy the requirements of this final rule. We do not have data on the number of foreign firms that export dietary supplements to the United States. The small number of foreign products in the FDA dietary supplement sales database (Ref. E18) suggests that relatively few foreign firms export dietary

supplements to the U.S. The foreign firms that will be most affected by the final rule are suppliers of dietary ingredients. Although suppliers of dietary ingredients are not directly covered by the final rule, the need of manufacturers to meet the ingredient specifications required by the final rule will indirectly affect foreign suppliers (as well as domestic suppliers).

(Comment 339) No comments were received on the economic analysis of the coverage of the 2003 CGMP Proposal.

4. Baseline Practices

a. Consumption. Baseline risks depend on baseline consumption of dietary supplements. Total sales in 2003 were about $20 billion (Ref. E4). Vitamins and minerals accounted for about 42 percent of sales. Sales of herbal supplements, which have not grown in recent years, were about half as large as sales of vitamin and minerals, accounting for 21 percent of the total. Amino acids, proteins, animal extracts, tea-like supplements, and other supplements not otherwise classified accounted for the remainder of sales in 2003.

(Comment 340) There were no comments on the consumption baseline.

b. Manufacturing. We contracted with RTI to conduct a survey of the dietary supplement industry to learn about both baseline (existing) manufacturing practices and the existing standards used for manufacturing dietary ingredients and dietary supplements (Ref. E3). A sample of 966 dietary supplement establishments from the DS-EED database was selected from an estimated eligible population of 1,566 firms in the industry (the total number included 106 ingredient manufacturers, who are now excluded). We further classified the target firms by product and by size. The product categories were; (1) Vitamins and minerals; (2) amino acids and proteins; (3) herbals and botanicals, including extracts; and (4) supplements not already classified.

The Small Business Administration classifies companies as "small" based on the size of the entire company, including both parent and subsidiaries. If firms that manufacture dietary supplements have fewer than 500 employees, they are classified as small. In addition we classify firms with fewer than 20 employees as very small.

We received 238 completed surveys. Table 22 shows the number of completed surveys by product and by size of establishment.

Table 22. Number of Completed Surveys by Sampling Strata

	Size				
	Very Small (fewer than 20 employees	Small (20 to 499 employees	Large (500 or more employees	Unknown	Total
Vitamins and minerals	19	39	13	1	72
Amino acids, proteins	8	7	0	5	20
Herbals and botanicals, including extracts	58	25	0	30	113
Supplements not already classified	14	13	2	4	33
Total	99	84	15	40	238

(Comment 341) We received two comments on manufacturers' baseline practices. One comment expresses concern that, as the information is over three years old, it may no longer represent current industry practices. The second comment questions the way we calculated the number of dietary supplement

establishments that do not follow any CGMP models. In the 2003 CGMP Proposal, we state that survey data reflect that 36 percent of surveyed establishments do not follow any CGMP models. The comment points out that 26.5 percent of firms responded "no" to the question, "Does this plant follow a published GMP model for the dietary supplement products produced at this plant?" Furthermore, of the 63 that answered "no", "at least" 29 of the firms provided responses indicating the reason they do not follow a published GMP is that they did not manufacture dietary supplement products.

(Response) Although the survey responses are now close to 5 years old, they represent the best information we have on the industry and its practices. We have, however, adjusted our estimated costs to reflect the correction of the results from the original survey.

5. Baseline Risk

The current number of illnesses caused by poor manufacturing practices requires data linking illnesses to poor practices. Industry is not required to report these data.

We looked at many sources for information, including medical and other literature on adverse events, information from poison control centers, reports to the agency, newspaper and magazine articles, and surveys of users. The literature review was conducted using Medline, Healthstar, Aidsline, Cancerlit, and OldMedline (Ref. E5). We found evidence of many adverse events associated with dietary supplements. For example, one survey found that 12 percent of consumers (about 11.9 million) who have used an herbal remedy claim to have suffered from side effects or other adverse reactions (Ref. E6). In another survey, 46 percent of respondents answered that people get sick from dietary supplements "often" or "sometimes" (Ref. E1). In 2003, the American Association of Poison Control Centers received 24,412 reports on herbal dietary supplements and 57,801 reports on vitamin and mineral supplements, with 8,653 of the herbal and 5,669 or the vitamin and mineral reports treated in health care facilities (Ref. E7). In addition, we have received many voluntary reports of illnesses caused by dietary supplements (Ref. E8).

The vast majority of the illnesses described in the sources we consulted, however, are reported as associated with the

ingredients used in the products themselves, not with contamination or other results of poor manufacturing processes. Most of the reports from poison control centers on vitamins and minerals, for example, involved inappropriate ingestion by children (Ref. E7). We have no direct evidence on how many illnesses can be attributed to manufacturing processes. The anecdotal evidence described elsewhere in the preamble suggests that many illnesses could have been caused by poor manufacturing processes, but there are only examples of evidence that explicitly links illnesses to these manufacturing processes. Examples of illness that were linked directly to poor manufacturing practices include vitamin D toxicity from excessive vitamin D in multivitamins and cardiac glycoside poisoning from botanical dietary supplements contaminated with *Digitalis Lanata*.

With no direct evidence on the number of illnesses caused by poor manufacturing practices, we had to use an indirect approach. We based the approach on our recall records. Class 1 and class 2 recalls all involve defective products that could have caused illness if ingested. Although the recall data cannot be linked directly to illness data, we have found

anecdotes, surveys, and some medical literature on illnesses that could be caused by avoidable manufacturing mistakes. We have recall data that show that manufacturing mistakes exist, so we can construct a plausible link between manufacturing mistakes and potential illnesses or injuries. The number of illnesses associated with a recall is both variable and uncertain, and could be anything from zero to quite large. Based on data from FDA recalls, we concluded that one reported illness per recall is a plausible average, so we assumed that a recalled product could be a proxy for a single reported illness associated with a defective product. We did not receive any comments disputing the appropriateness of this assumption. In particular, we did not receive any comments from industry, which may have information not available to us, as to adverse events associated with their products.

Because there are no well established systems for the notification of adverse health events related to dietary supplements, we assume that the total number of illnesses caused by poor manufacturing practices is substantially greater than the number reported. Based on data for drug and vaccine reporting rates in other studies, we concluded that for dietary

supplements, reported illnesses represent at best approximately 1 percent of total illnesses (Ref. E9). We assume that reporting adverse health events due to poorly manufactured dietary supplements occurs at the same rate as reporting adverse health events caused for other reasons by dietary supplements. We show the sensitivity of benefits to the choice of multiplier below, in the uncertainty and sensitivity analysis of our results.

We assume that the reported class 1 and class 2 recalls that occurred from 1990 through 1999 represent the number and type of recalls that will occur in the future but for compliance with the final rule. From 1990 through 1999, we received reports on an annual average of 13 class 1 and class 2 recalls of dietary supplements. If each recall is a proxy for a reported illness, then the total number of illnesses per year is approximately 1,300. We recognize that our procedure generated uncertain estimates of the number of illnesses. We estimate that the monetary value of the health costs associated with an illness come from: (1) The loss of productivity, (2) pain and suffering, and (3) expenditures on medical treatment. We measured lost productivity indirectly with measures of

functional state, which includes measures of physical function. We estimated the losses caused by pain and suffering with a symptom-problem index. We used direct measures of medical costs, such as payments to physicians and hospitals. We obtained data on the cost of a hospital day and other medical costs from the Health Care Cost and Utilization Project's Nationwide Inpatient Sample, administered by the HHS Agency for Healthcare Research and Quality (Ref. E10).

Table 23 contains summaries of our measures of the health effects potentially caused by known instances of defective products associated with poor manufacturing processes. We estimated the health loss per day for the different levels of illness severity by summing the lost productivity (as measured by functional state) and the loss from pain and suffering (as measured by the symptom-problem index[1]). These losses per day can be interpreted as the difference between a day of normal health and a day of suffering from the health conditions caused by these defective products. The numerical scale is a relative

[1]Functional Status Code is a measure of lost mobility (MOB), physical activity (PAC) and social activity (SOC). Lost MOB might mean an inability to drive a car. Lost PAC might mean walking with physical limitations. Lost SOC might mean self-care is not possible. Symptom-problem health utility index is a weighted measure of the cost of each symptom. For example, a sick or upset stomach leads to an estimated loss of 0.290 per day.

baseline that rests on the notion of a quality-adjusted life day (QALD). The QALD for a day of normal health equals 1; the QALD for death equals 0. The loss of quality adjusted life days per illness equals the daily loss multiplied by the number of days the illness lasts. We converted quality adjusted life days to dollars by multiplying the index numbers by the dollar value of a quality adjusted life day. We computed the monetary value of a quality adjusted life day using three values derived from three different values for a quality adjusted life year: $100,000, $300,000, and $500,000. These yield values per day of $274, $822, and $1,370. Our base measures use $822; we show the effects of using other values in the sensitivity analysis.

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The hazards that occurred between 1990 and 1999 are not necessarily the same hazards that would occur today. For example, botulism is rare and may no longer be a hazard associated with dietary supplements but recalls involving botulism represent generic examples of adulteration that could occur with other substances in the absence of good manufacturing practices.

(Comment 342) We received a comment that took issue with the way the recalls are counted. The comment asserts it is more appropriate to count each recall action as a separate recall, regardless of the number of different products affected.

The same comment criticizes the inclusion of the outbreak of eosinophilia-myalgia syndrome (EMS) in the table of what is characterized as "ordinary" recalls, since this case is analyzed separately as an example of a "rare catastrophic event". The comment states that the outbreak of digitalis should also have not been included in the recall list because it also was a rare event. The comment asserts that FDA announcements and media attention should have led to full reporting of any adverse events.

Other comments generally refer to risk associated with dietary supplements. One comment states that botanical supplements pose minimal risk if dispensed directly to a patient rather than used in an unsupervised setting, and that toxicology and adverse event reports indicate that end-of-process adulteration in herbal clinics is rare. By contrast, another comment states that adverse events related to dietary supplement use led to hospital admissions at one location and that reports of misbranded and adulterated dietary supplements are common.

(Response) We are not changing the way we count recalls. Each different product recalled under a recall action will continue to be counted as a separate product recall. How product recalls are counted, however, does not affect the analysis. The method used in this analysis corresponds to an average of about one reported illness per recall. If we changed the way we counted recalls so as to reduce the number of recalls, the average reported illnesses per recall would rise in proportion. The estimated benefits would not change.

We are no longer including the outbreak of EMS in our analysis of benefits. The product recalls associated with eosinophilia-myalgia syndrome occurred several years after the

outbreak that we are now excluding. The continued benefit associated with preventing EMS is associated with incorporating quality controls aimed at such hazards.

6. Benefits

The benefits of this final rule come from ensuring the quality of dietary supplements. Dietary supplements should contain the listed ingredients in the listed amounts in product forms that disintegrate and dissolve. Dietary supplements should not contain any contaminants that would adulterate the product under section 402(a)(1), (a)(2), (a)(3), or (a)(4) of the act.

Estimating the benefits of preventing adulteration and contamination is straightforward, at least in theory. These benefits are the value of reducing the risk of the acute illnesses and longer-term complications associated with physical, chemical, and microbiological contamination (see table 23). The direct value of preventing recalls is another source of benefits from preventing adulteration and contamination. We estimate the benefits of preventing adulteration and contamination by first estimating (based on recall data) the number and kinds of illnesses prevented, and then placing a

value on preventing those illnesses. We include the recall costs avoided by industry as additional benefits of preventing adulteration and contamination.

Estimating the value of ensuring the quality of the dietary supplements and that they are manufactured according to their specifications is difficult because we lack the necessary data on what is missing and how what is missing affects public health. These benefits are the value of reducing the risk of chronic illnesses and chronic conditions associated with nutritional deficiencies (see table 25). Some dietary supplements have authorized health claim labeling that allows them to state their products may reduce the risk of chronic illnesses or conditions. Ensuring that those supplements are manufactured consistently according to the appropriate specifications will increase their effectiveness in reducing the risk of chronic illnesses. In this analysis, we describe those benefits but do not quantify them.

The benefits from the final rule, then, will be:

- Reduced health costs associated with a reduced number of acute illnesses (quantified);
- Fewer product recalls (quantified); and

- Reduced health costs associated with a reduced number of chronic illnesses and conditions(not quantified).

(Comment 343) We received many comments on the estimated benefits. Although we did receive comments that stated the rule would benefit consumers by enhancing public confidence in dietary supplements, many comments state that the estimated benefits in the 2003 CGMP Proposal were overstated. In addition, one comment states that our estimates of benefits are double counted, because the outbreak of EMS was included in the measure of benefits from preventing a large catastrophic event as well as total benefits of reduction of illnesses measured by recalls. Furthermore, comments critical of the benefits state the search cost model used in the analysis is not applicable or the benefits of reduced search costs do not exist, we lack evidence with which to base the estimate of reduced health care costs from elimination of rare catastrophic events, and recalls will not fall to zero as a result of implementing CGMPs.

(Response) We agree with the comment that benefits were overstated because of the inclusion of the outbreak of EMS. We no longer include the value of preventing that or similar outbreaks in our estimate of benefits. Although we do not agree

with the comments on the applicability of the search model as a measure of benefits, the difficulties associated with quantifying those benefits have led us to replace the search model with a qualitative description.

We now explain each of the 3 sources of benefits: Reduced acute illnesses, fewer recalls, and reduced chronic illnesses and conditions.

a. Reduced health costs associated with a reduced number of acute illnesses. The final rule will help ensure the quality of dietary supplements, which will lead to improved safety of dietary supplements, reducing the probability of acute illness or deaths caused by manufacturing problems. We estimated the reduction of acute illnesses by using our recall records as evidence of possible illnesses; class 1 and class 2 recalls of dietary supplements all involved adulterated products that could have caused illness if ingested. In the 2003 CGMP Proposal we estimated the reduction of illnesses from preventing catastrophic events by using the public health effects of the outbreak of EMS that resulted from consumption of contaminated L-Tryptophan. We agree with comments questioning the applicability of this outbreak to CGMP, so we are no longer

including the value of preventing this outbreak as a benefit of this rule.

We estimated the annual expected health benefits for acute illnesses prevented by taking the values of preventing particular illnesses and weighing them by their likely incidence as indicated by recall data. The acute illnesses prevented that we use to estimate benefits are not actual illnesses, but statistical illnesses (defined as the probability of illness multiplied by the population at risk) prevented by the reduction in risk associated with this final rule. These recalls indicate recurring failures to ensure the quality of dietary supplements. Although each class 1 and 2 recall is estimated to have resulted in some illnesses (which may have triggered the recall), there may also be other manufacturing problems that did not lead to recalls but that did lead to illness. Both situations are part of the baseline number of illnesses and deaths estimated.

We computed the expected health benefits from preventing a single illness (of any type) associated with a recall as a weighted average of all potential illnesses. We then calculated the average health benefits of preventing a single illness associated with a class 1 or a class 2 recall as:

Health costs prevented = (QALD x days ill x value per QALD) + medical costs

We define QALD as the average quality adjusted life day per illness; we computed the average by weighting the quality adjusted life days lost for the probability of each level of severity (mild, moderate, severe, or fatal) by the frequency of that level of severity.

We calculated the weighted average benefit for all class 1 illnesses and multiplied it by the estimated number of class 1 illnesses prevented. We then repeated the procedure for class 2 illnesses prevented. The health benefits are therefore estimated as:

Health benefits = (average benefit per class 1 illness prevented) x (estimated annual number of class 1 illnesses prevented) + (average benefit per class 2 illness prevented) x (estimated annual number of class 2 illnesses prevented).

Table 24. Health Benefits Estimated Using Recall Data

Estimated total number of acute illnesses prevented	1,300

Estimated number of acute illnesses associated with class 1 recalls prevented	600
Estimated number of acute illnesses associated with class 2 recalls prevented	700
Dollar estimate of health benefit for preventing an acute illness associated with a class 1 recall	$65,000
Dollar estimate of health benefit for preventing an acute illness associated with a class 2 recall	$6,500
Estimated dollar estimate of annual health benefits, recall base	$44 million

To estimate the number of acute illnesses prevented, we started with the average number of products recalled per year for the decade 1990 to 1999. The yearly averages for the decade were six class 1 recalls and seven class 2 recalls. As discussed above, we then assumed that these recalls represented about 1 percent of all acute illnesses caused by the manufacturing problems leading to the recalls. With that assumption, we estimated that the recalls represented about 600 acute illnesses from class 1 recalls and 700 acute illnesses

from class 2 recalls.[2] The illnesses used to estimate the benefits of the final rule represent a sample of acute illnesses that could occur without this final rule. We assume that the benefits computed for the average year from the decade 1990-1999 represent the annual average benefits we should expect in the future. We do not assume that the acute illnesses prevented in the future will be identical to those that occurred during 1990-1999. In the sensitivity analysis, we show the effects of substituting the annual average for 2000-2003.

(Comment 344) We received comments critical of the estimates of reduced illness due to recalls. One comment points out that drugs, despite having stringent CGMP requirements, have a higher rate of recalls than dietary supplements, thus providing evidence that such requirements do not necessarily reduce recalls. Expanding on this thought, other comments state that we seem to assume that new CGMP requirements will reduce

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[2] We used a probability distribution to represent the uncertainty associated with the number of illnesses. We modeled the number of illnesses prevented for each class as the average number of recalled products plus a negative binomial distribution representing unknown cases. The negative binomial distribution estimates the number of failures (unknown cases) that will occur before some number of successes (known cases) for a given probability of success. In the negative binomial distribution, we assumed that the numbers of recalled products were reported cases and that the probability of reporting equaled 1 percent (Ref. E9). The result is that the mean estimated number of illnesses is 100 times the reported number of recalls.

human error to zero and no more recalls will occur, which is said to be unrealistic.

As discussed earlier in this document, the agency received a comment disagreeing with how the agency counts recalls. Again, this comment expresses belief that each recall action should be counted as a single recall, regardless of the number of products affected.

Other comments express concern about the 100-fold multiplier used to estimate the costs related to recall-associated illnesses. The comment states that we, besides referencing Walker (2000)(Ref. 9 in 2003 CGMP Proposal), have no other information to substantiate the use of the 100-fold multiplier and therefore are being arbitrary. Any other number could be as accurate. In addition, other comments state that it is difficult to believe that the multiplier would be applicable to recalls associated with Klebsiella pneumonia and selenium poisoning, and L-tryptophan, because the severity of the illnesses would certainly have been associated with the highly publicized recalls; that is, they would not have gone unreported.

Some comments present recalculated benefits. One comment estimates benefits from fewer illnesses as a result of the 2003 CGMP Proposal to be $10.9 million, rather than our estimate in the analysis of the 2003 CGMP Proposal of $39 million. This new estimate was arrived at by taking into account what was characterized as double-counted benefits which, as mentioned earlier, were characterized as the inclusion of EMS in the measure of benefits from preventing a large catastrophic event as well as total benefits of reduction of illnesses measured by recalls. Another comment re-estimates the benefits as $16 million. This estimate was calculated assuming 100 percent of potential illnesses related to Klebsiella pneumonia were classified as severe (with none classified as deaths), and 50 percent of illnesses associated with the selenium recall were classified as serious and none were classified as deaths. This comment also disagrees with the assumption that 3 percent of the 100 potentially ill from the recall associated with undeclared ephedra would have died. Furthermore, this comment adjusts the benefits to take into account recalls that this commenter felt were erroneously included in the calculation of benefits from reduced illnesses.

(Response) We have not seen any new data or other information that would lead us to change the 100-fold multiplier. The multiplier implicitly assumes that the more severe illnesses are more likely to be reported; the average reporting rate for all adverse events is assumed to be about 1 percent. The average incorporates higher reporting rates for more severe illnesses, and lower reporting rates for less severe illnesses.

The comments on the severity weights for Klebsiella pneumonia and ephedra did not persuade us to change these estimates. We based the estimates on the outcomes for severe events associated with these hazards. The Klebsiella weights come from the medical literature (Ref. E5); the ephedra weights are based on adverse events involving ephedrine alkaloids.

The comparison of drug recalls to dietary supplement recalls is not convincing. The drug industry is far larger than the dietary supplement industry. Expenditures on prescription drugs exceeded $200 billion in 2003. More to the point, most drug recalls are not the result of a failure of CGMPs.

(Comment 345) We received many comments regarding the use of the outbreak of EMS in 1989 as a basis for estimating health

benefits from preventing a catastrophic event. The majority of the comments assert that CGMPs would not have prevented the outbreak. One comment expands this assertion by stating our claim that testing requirements would reduce the probability that contaminated ingredients would be released to the public is incorrect, because it was not known what, if any, contaminants caused the outbreak. Secondly, the comment states that our claim that complaint files would allow for fast identification of an adverse health event is also incorrect because the victims of EMS did not know the L-tryptophan was the cause of their illnesses.

Two other comments question the periodicity for a cycle of potential catastrophic events due to dietary supplements. One comment suggests a period of 70 years rather than our 30 years. The other comment does not suggest a period but rather states that, since we have no data to support the cycle of 30 years, and we admit it is difficult to know how likely rare events are, it is possible that the total projected benefit could be zero.

Lastly, other comments state that the benefits from preventing a rare catastrophic event are double counted. These comments state these benefits are double counted because they

are also included in the estimation of benefits from reduced recalls.

(Response) As stated above, we are no longer including estimated benefits from preventing a rare catastrophic event in the analysis of benefits. We continue to include the benefits of preventing cases of EMS in the annual health benefits, because several recalls associated with this hazard took place during the 1990-99 period.

b. Fewer products recalled. Implementation of the final rule will reduce the number of adulterated products distributed to the public, which will reduce the number of products recalled. Process controls and better record keeping will increase the ability of establishments to produce dietary supplements according to specifications and to identify problems before distribution. If adulterated products are caught before they are distributed or earlier in the production process, they will not need to be recalled.

To estimate the direct benefits from fewer recalled adulterated dietary supplements, we estimate the number of annual recalls of dietary supplements that would be prevented by adherence to CGMP requirements in the final rule. From 1990 to

1999, FDA received reports on an average of 20 recalls per year (Ref. E5). The average figure reported here includes class 3 recalls. The number of units of dietary supplements for each recalled product varied, so we used a distribution per recalled product of 1,000 units to 34,000 units (Ref. E5). Product price also varies, with most prices falling between $5 per unit and $9 per unit; we used a most likely price of $7.70 per unit. We also include an adjustment for the goodwill lost by the establishment as a result of the recall. We multiply the direct cost of the recall by two in order to include the lost goodwill. The result is an estimated savings of $1.5 million in direct costs and $1.5 million in goodwill, for a total savings of about $3 million per year.

(Comment 346) We received several comments on our estimates of the reduction in recalls. As noted previously, a comment generally states that drugs, despite having stringent CGMP requirements, have a higher rate of recalls than dietary supplements, thus providing evidence that CGMPs do not necessarily reduce recalls. Again, other comments state that we seem to hold the unrealistic assumption that the final rule will reduce human error to zero and no more recalls will occur.

Another comment points out that the assumption that the final rule would cause the discovery of all adulteration is inconsistent with the requirement that firms keep complaint files. If the rule eliminates adulteration, the comment states, then there should be no complaints to report.

Again, we received a comment disagreeing with how we count recalls, which expresses the belief that each recall action should be counted as a single recall, regardless of the number of products affected.

(Response) As stated earlier in this section, we did not receive sufficient information to warrant changing the way we counts recalls. Each separate product affected by a recall action will be counted as a single recall. We do not believe that recalls will fall to zero. We assume that the recalls identified as being preventable by this final rule will fall to zero, but that mistakes and other hazards will continue to generate recalls. In the sensitivity analysis, however, we show the effects of different levels of effectiveness in preventing recalls.

As we explained, recalls of drugs are not comparable to recalls of dietary supplements and do not typically involve failure of the CGMP requirements.

c. Reduced health costs associated with a reduced number of chronic illnesses and conditions. We cannot quantify the value of ensuring that dietary supplements contain everything in the established specifications (and nothing that is not in the specifications) because we lack the necessary data on what is missing and how what is missing affects public health The public health benefits are derived from the reduced number of chronic illnesses and conditions. These benefits may arise from known nutritional effects or from uncertain nutritional effects.

d. Benefits From Known Nutritional Effects. Many of the nutritional benefits of vitamins and minerals are known and well-documented. For example, *the Dietary Guidelines for Americans, 2005* states that dietary supplements can be used to help meet the recommended intakes of vitamin B_{12}, folic acid, and vitamin D (Ref. E11). The Institute of Medicine's *Dietary Reference Intakes* include statements that supplements can be sources of several vitamins and minerals (Ref. E12). We have recognized the use of supplements in authorized health claims

for calcium and osteoporosis (§ 101.72) and folic acid and neural tube defects (§ 101.79).

In the following table, we list some of the health benefits associated with the consumption of various dietary supplements.

Table 25. Selected Health Benefits from Dietary Supplements

Dietary supplement	Who should take it	What it does
Folic acid	Women of child-bearing age	Reduces the risk of neural tube defects
Calcium	Children and adults	Reduces the risk of osteoporosis
Iron	Adolescent females and women of child-bearing age	Reduces the risk of anemia
Vitamin D	Children and adults; persons with dark skin, or with too little exposure to sunlight	Reduces the risk of osteoporosis
Vitamin B_{12}	Persons over the age of 50	Reduces the risk of anemia

e. Benefits from uncertain nutritional effects. We do not know the full range of effects (or lack of effects) of most dietary supplements. Vitamins and minerals with known nutritional effects in supplement form may have other effects that we have yet to discover. Our uncertainty is particularly large with respect to the nutritional effects of herbal and

botanical supplements. The evidence is still too mixed and incomplete to determine the effects of most of these substances. If, however, herbal dietary supplements do indeed have significant effects on the risk of chronic illnesses and conditions, then if the final rule ensures that the supplements consistently meet their specifications, we should add those benefits to those from supplements having known nutritional effects.

The benefits of this final rule that we can identify are those associated with the known effects. The product deficiency might be, for example, that packages contain some percentage less or more of the necessary ingredient (such as calcium) than what is listed on the label. The relationship between the reduced or excess amount of the ingredient and the probability of chronic illness would also have to be taken into account in order to determine the risk associated with the product deficiencies. The increase in the probability of chronic illnesses may be less than, the same, or more than the reduction in the amount of the ingredient. The increase in the probability of chronic illness would also depend on how long the supplement was deficient in the ingredient. Suppose, for

example, that a calcium supplement contains 10 percent less calcium than it should for one year. If the average consumer takes calcium supplements for 20 years, would the one-year deficiency of 10 percent increase the probability of osteoporosis by more or less than 0.5 percent (10 percent x (1/20))?

With sufficient data and other information, we would estimate risk reduction for some dietary supplements based on the chronic illness or condition that would help prevent. The model for risk reduction would start with the situation before the final rule, where the number of chronic illness prevented by dietary supplements is:

> Number of persons at risk for the chronic illness x percent of persons at risk who take dietary supplements (before the final rule) x reduction in the risk of chronic illnesses if person at risk consumes dietary supplements (before the final rule)

After the final rule takes effect, the number of chronic illnesses prevented would be:

Number of persons at risk for the chronic illness x percent of persons at risk who take dietary supplements (after the final rule) x reduction in the risk of chronic illnesses if person at risk consumes dietary supplements (after the final rule)

The number of chronic illnesses prevented by the final rule would be:

Number of persons at risk for the chronic illness x change in percent of persons at risk who take dietary supplements x change in the reduction in the risk of chronic illnesses if person at risk consumes dietary supplements

For some chronic illnesses or conditions, the final rule can be expected to change the numbers of persons consuming dietary supplements and the reduction in the probability of chronic illness brought about by consuming dietary supplements.

If we could determine the change in the number of chronic illnesses prevented by dietary supplements as a result of this final rule, we could estimate benefits by multiplying the additional number of chronic illnesses prevented by the value of

preventing those illnesses. The values consumers place on preventing illness differ across illnesses and across consumers, and are related to the reasons they use dietary supplements. We will illustrate the method with two examples: Calcium and osteoporosis and folic acid and neural tube defects.

Calcium and osteoporosis. Many consumers take calcium supplements to reduce the probability of osteoporosis, which afflicts as many as 10 million people over age 50 (about 8 million women and 2 million men). An additional 34 million men and women may be at risk for developing osteoporosis (Ref. E14). If ensuring that calcium supplements contain what they should reduces the risk of osteoporosis, the total osteoporosis health benefits associated with the final rule will be the number of cases prevented multiplied by the health costs per case. We estimated the health costs per case as the sum of the direct medical costs, the value of functional disability, and the value of the pain and suffering associated with the illness. Cases range in severity from mild to severe. A mild case, for example, might lead to a loss of utility (measured as quality adjusted life years – a year of life adjusted for the individual's health status) of 0.14 per year for 9 years. If we

apply a discount rate of 7 percent to the years the condition lasts, the loss of quality adjusted life years is about 0.9 (6.5 discounted years x 0.14 lost utility per year). In other rulemakings we have used a range of values for a quality adjusted life year; the range has been from $100,000 to $500,000, with a medium monetary value of $300,000 (68 FR 41434, July 11, 2003). With a value per year of $300,000, the value of preventing a mild case is about $270,000 (0.9 x $300,000).

A severe case, by contrast, can lead to fractures and permanent disability. Also, osteoporosis in women can occur at early ages and last decades. If someone suffers from osteoporosis for 30 years, the discounted quality adjusted life years lost would be 6.9 (12.4 discounted years x 0.56 lost utility per year). We estimate that medical costs for a severe case can be over $17,000. The value of preventing a severe, long-lasting case is therefore about $2.1 million ((6.9 x $300,000) + $17,000).

Folic acid and neural tube defects. Many women of child-bearing age take dietary supplements to help ensure their own

health and the health of their children should they become pregnant. For example, 40 percent of women aged 18 to 45 take supplements containing folic acid, which may reduce the probability that children will be borne with neural tube defects (Ref. E15). Neural tube defects affect the spine (spina bifida) and the brain (anencephaly). About 3,000 pregnancies are affected each year (Ref. E15).

The benefit of ensuring that folic acid supplements contain what they should equals the population at risk multiplied by the reduction in the probability of neural tube defects, multiplied by the value of preventing a neural tube defect. Neural tube defects involve large medical expenses, and either early death or permanent disability. The lifetime medical costs alone are between $400,000 and $500,000 for spina bifida (Ref. E17, with values updated). In recent rulemakings, we have used $5 million to $6.5 million as the value of a statistical life, defined as the willingness to pay for reductions in small risks of premature death. Preventing a statistical death from anencephaly would therefore generate benefits of $5 million to $6.5 million. For spina bifida, one estimate is that an average case leads to a loss of more than 15 quality adjusted life

years, for a monetized loss of close to $5 million for a non-fatal case if valued at $300,000 per quality adjusted life year (Ref. E16). The value of preventing a case of spina bifida, then, is the sum of medical costs and the value of a saving the quality adjusted life years, or about $5 million ($450 million value of quality adjusted life years + $500,000 direct medical costs).

Estimating the total benefits of this final rule requires estimates of the numbers of chronic illnesses and conditions whose incidence can be further reduced by ensuring that dietary supplements contain what they should. Because we have no information on the baseline number of chronic illnesses caused by deficient ingredients, or on the change in the likelihood of chronic illness that will occur as a result of the provisions of this final rule, we cannot estimate the full benefits of ensuring that dietary supplements contain what they should. Our quantified benefits for this final rule must therefore consist entirely of the benefits from reducing the risks of acute illnesses and reducing the number of product recalls. The total benefits will be larger by an amount we are not able to quantify.

(Comment 347) We received many comments about the estimated benefits as measured by the value of hypothetical search time.

(Response) We are no longer using the search model.

f. Total benefits. The total benefits from the final rule are the sum of the value of health benefits from fewer acute illnesses, the value of fewer product recalls, and the value of the health benefits from fewer chronic illnesses. Table 26 shows the total benefits.

(Comment 348) One comment states that our total estimated benefits could be as little as $21 million.

(Response) Our current estimate of total quantified benefits is $48 million per year, once the final rule takes full effect. In addition, as discussed above, there are benefits to this rule that have not been quantified. The unqualified benefits estimate is the mean of a range of estimates based on assumptions about reporting rates and the effectiveness of the final rule. In the uncertainty and sensitivity analyses in section XXIV.B.9, we show how uncertainty and different assumptions generate higher or lower quantified benefits. Using

plausible assumptions about the uncertain variables, we estimate that total quantified benefits most likely fall within a range of $10 million to $80 million per year.

Table 26. Summary of Annual Benefits

Benefits	Mean
Fewer acute illnesses	$44 million
Fewer product recalls	$3 million
Fewer chronic illnesses	Not quantified
Total quantified benefits	$48 million

7. Costs

The same changes in manufacturing practices that produce benefits also have costs, the opportunity costs of reducing some of what they are now doing. For example, firms may spend fewer resources on worker safety, product development and marketing, or testing the efficacy of their products. The final rule will require dietary supplement establishments to adopt some new practices in order to manufacture, package, label, or hold their products in compliance with CGMP requirements. In some cases, establishments will make capital improvements to the physical plant, add or replace equipment or controls, perform additional maintenance, establish written procedures, keep records, carry out tests, monitor production and process controls, or execute a variety of additional tasks that they may not have previously

performed. Not all firms will comply – some will go out of business or move their plants to other countries and not sell their product in the United States. We estimated the additional costs of production associated with the final rule and the leading regulatory options using the survey (Ref. E3) to estimate baseline manufacturing practices.

a. Description of the costs. To estimate costs for the dietary supplement industry, we initially divided the industry into four product categories and three size categories. Because the survey showed that there were only a few establishments in some categories, we consolidated the size and product into three size categories. The size categories were:

- Very small (fewer than 20 employees)
- Small (20 to 499 employees)
- Large (500 or more employees)

Although this consolidation glosses over the important differences across products, the purpose is to estimate the broad average costs of the rule.

For each size category, we constructed a cost model that included every provision of the final rule. We then attached a cost to each provision that had an additional activity

associated with it. Most provisions did not have costs attached to them, because they were either descriptive or the costs were included elsewhere.

The costs will be the marginal, or additional costs of the activities producers undertake in response to the provisions of the final rule. In the cost model, we expressed the cost as cost per unit, with the unit being the establishment, the number of employees, or the annual number of batches produced or affected.

b. Summary of general comments on costs. We received many comments on the costs of the 2003 CGMP Proposal. Many of the comments were general in nature and addressed the belief that our economic analysis underestimated the total costs of the 2003 CGMP Proposal, both first year costs and annual costs. Numerous comments point to the rule's testing requirements as the main cause of the high costs. Comments also state that the analysis underestimates costs of hiring new workers, capital equipment, and holding and distributing costs. In addition, some comments point out that the economic analysis did not include estimates of costs of holding reserve samples and tracking product complaints.

As a result of the 2003 CGMP Proposal, comments assert, product choice would decline, prices of existing products would increase, and many businesses -- particularly small businesses -- would be forced to shut down. One comment states there could be a decrease in spending on research and development. Some comments state that the burden on business could be alleviated by allowing the use of certificates of analysis for incoming raw materials and using a statistical, or more flexible, testing regime instead of requiring final product testing on all batches.

A comment from a trade association representing ingredient suppliers and manufacturers in the dietary supplement industry accepts our assumptions on the following variables:

- The number of control points
- The average number of ingredients per product
- The average cost per test

Other comments, however, state that the average number of ingredients is higher than estimated and that the average cost per test is higher than estimated; one comment from a manufacturer states that its average cost was 2.5 times our estimate. These comments came from self-described small firms.

(Comment 349) One comment states that we failed to consider start-up costs.

(Response) We include start-up costs (also referred to as set-up or one-time costs) throughout this analysis.

(Comment 350) Many comments on the regulatory impact analysis targeted our estimates of firms' batches per year. Nearly all comments about batches state that our batch estimates are too low. For example, an industry trade groups claims our estimate of 309 batches per year for large firms is "implausibly low." The same comment states that the distribution of the number of batches per firm of 309, 554, and 223 for large, small, and very small firms, respectively, is "illogical" because it does not make sense that large firms would have fewer batches per year than small firms.

(Response) Due to a contractor's error, we used an inaccurate estimate of the annual number of batches in the analysis of the 2003 CGMP Proposal. The analysis of the final rule corrects for this error. The corrected estimates of the number of batches continue to show that small firms produce more batches than large firms. Comments from self-described small firms suggest that this distribution of batches is reasonable.

These comments state that many small firms produce many small batches of product.

(Comment 351) One comment states that we used faulty data in the economic analysis.

(Response) In accordance with our information quality guidelines, we have used the best available data in this analysis. As explained in the response to the previous comment, the survey results used in the analysis of the 2003 CGMP Proposal included an inaccurate estimate of the number of batches of dietary supplements produced. We use the corrected estimate in the analysis of this final rule.

(Comment 352) Some comments dispute the estimated testing costs. In particular, comments question our assumptions on:

- The number of tests required per batch;
- The number of tests already being performed;
- The costs to perform specific analytical tests; and
- The development of analytical methods.

(Response) The final rule reduces the number of required tests. In the final rule, we account for tests where no analytical methods have been developed. We now require fewer tests, although we anticipate that some testing will take place

associated with the creation of certificates of analysis required for component specifications and as verification for process controls. We now assume that the tests will be:

- One identity test for each shipment lot of incoming dietary ingredients (e.g., Vitamin C),
- Tests of subsets of shipment lots by supplier firms to create certificates of analysis for identity of other components (e.g., sugar),
- Tests of subsets of shipment lots for other specifications in the certificates of analysis,
- Tests of subsets of batches of dietary supplements for microbial, chemical, or physical contaminants,
- Tests of subsets of batches of dietary supplements for specifications, and
- Tests for meeting requirements that water used to manufacture dietary supplements complies with Federal, State, and local requirements and does not contaminate the dietary supplement.

We are not changing our estimate of the current prevalence of testing, which is based on the survey of manufacturers (Ref. E3). We would only revise this estimate in light of new data of comparable quality to that provided by the survey.

(Comment 353) We did receive two comments favorable to recordkeeping, stating that master and production batch records were good to adopt and that associated costs will be minimal. One of the comments states that the level of detail may be unrealistic for a small firm, but also states that any final regulation could be made more flexible for small manufacturers.

Although there were favorable comments, we received several comments critical of the recordkeeping requirements. These comments make general statements that the economic analysis underestimates the recordkeeping burden and some added that these requirements go beyond the CGMPs for food. In addition, several of the comments include firms' own estimates of costs of complying with the recordkeeping requirement. Comments estimate costs in the range of $11,000–$64,000.

(Response) The recordkeeping requirements in the final rule differ from the 2003 CGMP Proposal and are addressed in the revised costs below and in the Paperwork Reduction Act analysis.

(Comment 354) We received a favorable comment regarding the requirements for physical plant and equipment, saying that, although the costs would be moderate, the result would be higher

quality products. Another comment states that, although not unrealistic, the provision would be very costly.

Other comments are more critical. One comment estimates that renovation expenses would amount to approximately $600 million over the entire industry, as opposed to our estimate of $45 million. This comment states that the reason our estimates in the 2003 CGMP Proposal were too low is that we apply a reduction factor which assumes that 18 percent of very small firms, 10 percent of small firms and 1 percent of large firms will have to make capital improvements. It is more appropriate, the comment states, to assume that most facilities will need to renovate about 10 percent of their plant, regardless of firm size. In addition, the requirement that plants have smooth, hard surfaces on all floors, walls and ceilings is unrealistic and would add quite a bit of cost. The comment asserts no company will have such surfaces throughout the plant and, this is not a requirement in either the food or drug CGMP requirements. Other comments echo the belief that capital expenditures would be greater than our estimates and would be excessively burdensome. One comment estimates this cost at approximately $83,000 per facility.

The comment also estimates that a large firm that needs to expand its capacity could expect to incur costs of $240,000, as opposed to the $2,000 that the comment says we estimated for large firms. In addition, it is pointed out that equipment costs could be burdensome to small firms, which likely do not have well-equipped labs. This thought is affirmed by other comments that estimate that new equipment could cost anywhere from $50,000 to $1 million, with annual costs estimated between $15,000 and $100,000. In addition, expansion of laboratory space is estimated at $200 per square foot, as opposed to the agency's estimate of $50 per square foot. Lastly, one comment suggests we work with the Internal Revenue Service to allow for more rapid depreciation of facility costs to help small business make facility upgrades.

(Response) In the analysis of the 2003 CGMP Proposal, we estimated the number of firms needing to make capital expenditures associated with the rule as a distribution, with the parameters of the distribution determined by the size of the facility. We assume that if a firm does make a capital investment in response to the rule, it would affect about 10 percent of the plant. With an estimated cost of $50 per square

foot, and the average size of a very small plant of about 25,000 square feet, the cost per very small establishment making a capital investment would be about $125,000. With the average size of a small plant of about 70,000 square feet, the cost per small establishment making a capital investment would be about $350,000. With the average size of a large plant of about 600,000 square feet, the cost per large establishment making a capital investment would be about $3 million (Ref. E3). We assume that most facilities will not need to make capital investments to meet the sanitation requirements of this final rule as, according to the survey results, most establishments already meet the sanitation standards of this final rule. This would not be possible if their facilities were inadequate.

We estimated the capital costs as the costs of minor renovations to help meet sanitation requirements, not as the cost of (say) expanding the size of a laboratory or some other technically sophisticated change. Although some facilities may choose to expand laboratories, the testing requirements of this final rule should be able to be met by existing laboratory facilities within or outside of the manufacturing facilities.

Working with the Internal Revenue Service on depreciation is beyond the scope of our authority. We will provide advice on financing capital improvements through our small business representatives in the Office of Regulatory Affairs.

(Comment 355) Many comments address costs resulting from what industry describes as the exhaustive testing requirements outlined in the 2003 CGMP Proposal. Comments point out that the requirement to test every ingredient would be very costly for firms large and small, with many firms stating that they risk going out of business. In addition, several comments add that the testing requirements would do little to enhance product quality. Many comments assert that allowing the use of a certificate of analysis would reduce the amount of tests performed on a shipment of incoming raw materials, reducing redundant testing, and also reducing the risk that a firm may go out of business. Other comments state that allowing statistical testing regimes would also cut down on testing costs.

(Response) As we already have discussed in this section, we have reduced the amount of required testing in this final rule. The final rule requires testing the identity of every incoming dietary ingredient. However, the final rule allows for

use of certificates of analysis in place of identity tests of other components and other tests of incoming dietary ingredients and other components. The final rule also allows sound statistical testing regimes for finished products.

(Comment 356) One comment states that our cost estimates are based on the assumption of only two ingredient tests, an assumption which the comment calls into question. For multivitamins, one comment estimates about 8 separate tests and 16 separate assays, depending on the nutrients present.

(Response) In the analysis of this final rule, we assume one identity test per incoming shipment lot of dietary ingredients based on the revisions made to the final rule compared with the 2003 CGMP Proposal.

(Comment 357) Many comments include individual estimates of testing costs. For example, two comments estimate an average cost of about $100 per test, and other comments estimate averages as high as $360, as opposed to our estimate of about $60 per test. Several other comments claim that the costs of finished product testing alone would be “at least 100 times” greater than our estimates; other comments state that testing costs would almost equal the costs of manufacturing. One

comment estimates testing costs for firms of all sizes at $245 million, as opposed to our estimate of $24 million, although another contains estimates as high as $13.6 million annually for one firm. Two comments concede that some finished product testing may be necessary.

In addition, some comments state that our estimate of finished and raw material testing is off by a multiple of 3 to 6. One comment states that, for companies that have products which contain a large number of ingredients expensive to test, very large costs will be incurred. This comment also states that our cost estimates do not include in-process testing, which they claim the rule would clearly require. Specifically, our analysis suggests that an average of 2.5 in-process tests per batch are likely to be needed at critical control points. In addition, the comment maintains that our analysis showed that additional testing may be required for an average of 2.5 components of herbal products and 7.5 components of herbal products, but our estimates do not include costs of the tests. Finally, comments point out that, if the production system is properly controlled, then a "reduced schedule" of final product testing is justified and that focusing excessive resources on

end-product testing does not constitute GMP. Quality controls should be built into the production and process system from the beginning of the manufacturing process.

A comment also states that our estimates of firms that already test are inaccurate. The comment asserts that our estimates are overstated and they also think we have understated that proportion of finished batches not currently being tested. In addition, the comment claims that "even large firms that are testing 90 percent of their products are unlikely to be performing the exhaustive level of testing required by the 2003 CGMP Proposal, namely testing every component of every batch of finished product".

The comments point out that our cost estimates do not include estimates for the cost of developing methods of analysis for ingredients. At a minimum, one comment states this estimate should be $2 million (the cost of 100 methods at a minimum of $20,000 each). Several comments point out that often there are no existing scientifically valid analytical methods to test finished products, especially botanical products. Another comment states that costs of analytical testing are at least three times our estimate, and could be as high as eight times

our estimate. Because of this, many comments call for the use of a certificate of analysis in place of analytical testing.

Another comment states some unintended consequences could occur in the industry due to the testing requirements, including stress on the current contract laboratory facilities and in-house laboratories, and also increases in holding costs, due to changes in turn-around time at outside labs. Other comments point to the loss of product choice that could occur if the testing requirements force manufacturers to go out of business or discontinue certain products.

(Response) In response to comments, we have revised the testing requirements in the final rule. We also have revised our estimates of the costs of testing. In what follows, we describe the estimated number and costs of tests required by this final rule.

The final rule requires tests for identity for each incoming dietary ingredient. Estimating the number of tests per batch is complicated, because the tests are required on the shipment lots and we have data only on the number of batches of dietary supplements produced. For example, if a shipment lot of some ingredient is used in 6 batches of final products, it would

need to be tested for identity only once. The number of required identity tests per batch of final product will equal the number of dietary ingredients per batch, divided by the average number of batches per shipment lot (to account for the production of multiple batches of dietary supplements from single lots of components). In addition to the required identity tests, a subset of other components will be tested for identity (these tests are likely to be the responsibility of suppliers and need only be done once per batch no matter how many recipients of those batches).

The quantity and quality of evidence on the variables used to estimate the number of tests varies greatly. In this section, we explain the evidence and assumptions we used to construct the formulas for the number of tests.

Number of dietary ingredients. We based our measure of the number of dietary ingredients per product on a sample of almost 3,000 dietary supplement labels (Ref. E18). Although some ingredients may be missing from the labels and some listed ingredients may be missing from the products, the ingredient list represents the best evidence we have on what ingredients are used in dietary supplements. Although comments claimed that

we underestimated the number of ingredients, they offered no evidence that would persuade us to change our estimates, which are based on a sample representing at least 10 percent of the products in the market.

According to the sample of listed ingredients, vitamin and mineral products contain about 13 listed ingredients. Other dietary supplements, mainly herbals, contain about 4 listed ingredients (Ref. E18).

Number of unlisted components. Dietary supplements are manufactured using solvents, binders, and lubricants that may not show up in the final product. An industry source (Ref. E20) says that 4 to 6 unlisted components are typical per product, although fewer are certainly possible. The minimum number is zero. Based on industry data, we assume that the number of unlisted components would be zero to 6 for vitamins and minerals, and zero to 4 for herbal and other products.

Number of shipments (that is, shipment lots) of ingredients and unlisted components. We have no direct information on the number of shipment lots of dietary ingredients and other components. We also have no information on the number of shipments per lot or on the number of shipments per batch. It

is costly to store components, so some establishments may buy many small lots of dietary ingredients and other components rather than a few large lots. Crude botanical and other ingredients are inherently unstable and may lose their stability in even a short time unless costly temperature, humidity, and light controls are in place. We also know, however, that some dietary ingredient suppliers produce and ship ingredients in large lots. For dietary supplements produced using part of a large production run of a dietary ingredient, the number of batches per shipment lot could be large. Also, some producers buy a single large shipment lot of a raw material and use it in many batches. We assume that as many as 12 batches per shipment lot of dietary ingredient is a plausible maximum. Based on consultation with industry (Ref. E47), we assumed, in the cost calculation, that 1 was the minimum and 12 the maximum number of batches produced per lot, with 6.5 the average. We received no comments on our use of the assumption in the analysis of the proposed rule and continue to use it in our analysis of the final rule. In the sensitivity analysis, we show how costs change when we change the assumption.

Number of batches produced. We have survey results (Ref. E3) on the number of batches produced per establishment. Several comments stated that we underestimated the number of batches produced, which we found to be the case because of an erroneous calculation in the contractor's report. In the revised contract survey results, very small establishments produce an average of 444 (revised from 223) batches per year, small establishments produce an average of 2,436 (revised from 554) batches per year, and large establishments produce an average of 1,164 (revised from 309) batches per year.

Number of final product tests per batch. We have reduced the number of tests required for final products. We assume that establishments will test a representative sample of batches to ensure that the final products meet specifications. We do not specify any particular statistical sampling plan.

Costs per test. We estimate the costs per test partly with published prices of independent laboratories as posted on the Internet (Refs. E21 and E22), and partly from our conversations with FDA and industry experts on testing. Testing costs vary according to frequency and complexity. The more frequently technicians perform tests, the lower are the costs per test.

Many tests require sophisticated equipment, such as gas chromatography, high pressure liquid chromatography, distillation, extraction, various spectrophotometers, and other types of equipment. Using sophisticated equipment requires trained personnel. Even simple physical or organoleptic testing requires training or experienced personnel. The type of ingredient, compound, or product can also affect the cost because some are easily identified using routine or single step techniques and others require multiple steps or complex techniques, especially if there are similar products that can be mistaken for the products being identified. The type of defect tested for affects the cost; some defects can be found visually if they are found on the surface, but others are latent. Some tests require multiple samples or multiple steps. In addition, tests require taking and preparing samples, whose cost can vary.

The average cost per test is about $60, based on a range of costs we found on the Internet. This cost represents the full cost of carrying out a test, including collecting and storing the sample, the time for training the personnel who carry out the test, and any associated records. We assume that $20 per test represents a lower bound. Although some Internet prices

for tests are as high as $300, we assumed that with frequent testing $150 would be a more plausible upper bound average cost. The majority of listed prices fell into the $20 to $80 range, so we selected $50 (the midpoint) as most likely.

The number and cost of tests: summary. We estimate the number of tests required of the representative manufacturer as a weighted average of the number of tests required for vitamins and minerals and the number of tests required for all other supplements (which were mainly herbal products). The weights, as shown below, differ by size of manufacturer:

- 24 percent of very small manufacturers produce vitamins and minerals; 76 percent produce other dietary supplements.
- 42 percent of small manufacturers produce vitamins and minerals; 58 percent produce other dietary supplements.
- 69 percent of large manufacturers produce vitamins and minerals; 31 percent produce other dietary supplements.

Most establishments already conduct some tests, or send samples out for testing. We therefore adjusted the estimated testing costs of the final rule to include only required tests and to account for the testing costs currently borne voluntarily

by manufacturers. The survey results showed how many respondents were conducting various types of tests.

Table 27. Values Used to Estimate Testing Costs

Name	Value or Distribution Used	Source
Number of dietary ingredients per product batch	Vitamins and minerals--13 All other categories—4	Sample from 3,000 dietary supplement labels (Ref. E18)
Number of identity tests per dietary ingredient lot	1 identity test per ingredient lot	Based on requirements of final rule
Number of identity tests per other component lot	1 identity test per subset of component lots	Assumption based on use of certificates of analysis for ingredients
Number of tests for specifications per ingredient lot	1 to 5 tests per subset of ingredient lots	Assumption based on use of certificates of analysis for ingredients
Number of unlisted components	0 to 6 components for vitamins and minerals, 0 to 4 for herbal and other products	Ref. E20
Number of shipments (lots) of ingredients and unlisted components	1 to 12 batches per shipment lot of dietary ingredients	Assumption based on discussions with industry
Number of batches produced per year	Very small establishments-444 Small establishments-2,436 Large-1,164	Ref. E3
Number of final product tests per batch	1 test per subset	Based on requirements of the final rule
Costs per test	Beta pert distribution skewed rightward between $20 to $150; $50 most likely; $60 average	Refs. E21 and E22

(Comment 358) We received comments on labor costs that would be incurred as a result of the 2003 CGMP Proposal. All comments state that personnel costs will increase significantly.

One comment states that the average manufacturing wage we used to estimate labor costs, $15.65, does not reflect the true cost of additional labor, since higher skilled employees, such as quality control engineers and, as one comment asserts, PhD-level employees, will need to be hired to comply with the rule. This comment states that, including benefits, the wage actually ranges between $23.28 and $72.00 per hour, depending on skill. Other comments estimate additional annual labor costs ranging between $25,000 and $350,000.

(Response) We used more recent estimates to the average manufacturing wage of $16 per hour to estimate the cost of labor (Ref. E19). The comment that asserted Ph.D.-level employees are needed to comply with the rule, provided no basis for this assertion. We disagree that Ph.D. level workers are needed for the tasks required by this final rule because the costs estimated as labor costs all involved ordinary labor tasks such as sanitation, monitoring and record keeping. For more difficult or complicated tasks, we assume that more hours will be required. We assume that various tasks required by the final rule would take some number of hours per year, per batch of product, or per square foot of physical plant.

Estimating costs. We initially gathered information and made assumptions about the full cost of a provision. We then adjusted these estimates to account for the many activities already being carried out, as well other activities that would not have to be carried out by all establishments. We used the survey to estimate the likelihood that an establishment will incur a cost. To get an estimate of the average cost of a provision (adjusted for baseline activities) for each category, we multiply the average cost per establishment by the probability that the establishment will need to undertake the expense (one minus the probability that the establishment is already doing it). For each provision of the final rule, the simulation carried out the following calculation:

Cost per unit of analysis for each provision =
number of units of analysis per establishment x
probability that establishment incurs cost x
cost per provision per establishment

We estimate both a setup cost (a one-time fixed cost) of the provision and an annual recurring cost. To get the total

costs of the rule, we multiply the number of establishments in each size category (from the survey) by the average costs per establishment in that category. We then adjust for the establishments that did not respond to the survey but are believed to be in the industry. Two hundred thirty-eight establishments responded to the survey; we estimate that 1,566 firms are in the industry, including ingredient suppliers. The number of firms covered by most of the provisions will therefore be about 1,460.

We estimate total costs with the following calculation:

[Number of very small establishments x costs per very small establishment) +
(number of small establishments x costs per small establishment) +
(number of large establishments x costs per large establishment)] x
adjustment for establishments not in survey

The rule is complex and the industry is made up of very different kinds of firms, so cost estimates are averages with, in some cases, large variances. The cost per unit, number of

batches and employees, and probability that the establishment would incur the cost all contain uncertainty. The values in the table are used in the cost estimates, and are generated from multiple sources.

Table 28. Additional Values Used in Cost Calculations

Name	Value or Distribution Used	Source
Average wage per hour	$16	Employment Index, Bureau of Labor Statistics (Ref. E19)

Average size of establishments in square feet	very small = 24,674;
	small = 71,354;
	large = 596,000
		Ref. E3

Average number of employees	very small = 7.6;
	small = 95;
	large = 1,005
		Ref. E3

Procedures	8 to 16 hours set-up time for small firms; 30 to 40 hours for large firms; annual cost is 10 percent of setup time per provision	Ref. E23
Personnel sanitation	1 hour per week per worker	Assumption, based on requirements of final rule
Sanitation time for physical plant	1 hour per week for very small establishments; costs per small and large plants scaled in proportion to size of plant	Assumption, based on difference in average physical plant size
Sanitation supervisor	1 hour per week	Assumption, based on requirements of final rule
Pest control setup costs	$1,500 to $2,000 for very small establishments; $1,800 to $2,400 for small establishments; $2,600 to $3,400 for large establishments. Average for each size establishment was midpoint ($1,750, $2,100, $3,000)	Ref. E24

Pest control annual costs	$400 to $600 per month for very small establishments; $480 to $720 for small establishments; $700 to $1,000 for large establishments. Average for each size establishment was the midpoint ($500, $600, $850)	Ref. E24
Renovation cost	$50 per square foot; with 0 to 20 percent of physical plant to be renovated, with 10 percent most likely	Based on construction costs and square feet (Ref. E3)
Equipment replacement	For very small establishments, 0 to $1,000;costs per small and large plants scaled in proportion to size of plant	Assumption, based on size of establishments (Ref. E3)
Setup costs for automatic equipment	$500 for hardware, 16 hours	Software costs and assumptions about labor hours
Annual costs for automatic equipment	10 percent of set-up costs	Assumption based on requirements of the final rule
Sanitation of equipment and surfaces	5 hours per week for very small establishments; costs per small and large plants scaled in proportion to size of plant	Assumption based on average sizes of establishments (Ref. E3)
Holding products and dietary ingredients: capital requirements	Same as costs of equipment upgrades	Based on average sizes of establishments (Ref. E3)
Default probabilities that establishments are not currently acting in accordance with a provision	For very small establishments, 0.2; for small establishments, 0.05, for large establishments, 0.01	Based on results of survey for other practices (Ref. E3)

The total set-up costs for this final rule will be $37 million, spread out over the 36 months following the publication

date of the final rule. The annual costs, once the final rule is fully implemented, will be $150 million, with the 2 largest costs being $60 million for testing and $17 million for records. The estimated total cost is the mean of a range of estimates based on the data and assumptions described in tables _(8) and (9). In the uncertainty and sensitivity analyses below, we show how uncertainty and different assumptions generate higher or lower estimated costs. Using plausible assumptions about the uncertain variables, we estimate that total quantified costs most likely will fall within a range of $90 million to $300 million per year.

8. Summary of Benefits and Costs

We estimate that, once it is fully implemented, the annual quantified benefits from the final rule will be $10 million to $80 million, with a mean estimate of $48 million. However, there are potentially large benefits of the rule that we were not able to quantify. The annual costs will be $90 million to $300 million, with a mean estimate of $150 million. The rule will not be fully effective until 36 months after the publication date. Table 29 shows how the phase-in of the final

rule will generate the costs and benefits for the first 4 years. Table 30 shows the present and annualized values of costs and benefits over 20 years, calculated at discount rates of 3 percent and 7 percent. We have determined, based in part on the analysis presented here, that the benefits of this final rule justify the costs.

Table 29. Costs and Benefits by Year

	1st year	2nd year	3rd year	4th year
Costs (in millions)	$9	$136	$167	$150
Benefits (in millions	$2	$38	$48	$48

Table 30. Present and Annualized Values of Costs and Benefits

	Present value at 3 percent(in billions)	Present value at 7 percent(in billions)	Annualized Value over 20 years at 3 percent (in millions)	Annualized Value over 20 years at 7 percent (in millions)
Costs	$2.1	$1.5	$140	$138
Benefits	$0.66	$0.46	$44	$43

In table 31 we show the annual costs for each subpart of the regulation. We are unable to estimate benefits by subpart, because we estimate the benefits by type of benefit rather than

by provision of the final rule. We classify benefits as arising from preventing contamination and adulteration and from ensuring more consistently manufactured products. The provisions of the final rule contribute to both sources of benefits, but some contribute disproportionately to one or the other source. In the table, we indicate which source of benefits each subpart supports, but we do not quantify benefits by subpart.

Table 31. Costs and Benefits by Subpart

Subpart	Set-up cost (in millions)	Annual cost (in millions)	Benefit
A. General provisions	not applicable	not applicable	not applicable
B. Personnel	$1.0	$14.3	Preventing contamination and adulteration
C. Physical plant and grounds	$32.5	$17.8	Preventing contamination and adulteration
D. Equipment and utensils	$0.9	$1.4	Preventing contamination and adulteration
E. Establish production and process control system	$0.3	$70	Preventing contamination and adulteration and ensuring more consistently manufactured products

F. Quality control unit	negligible	$1.1	Preventing contamination and adulteration and ensuring more consistently manufactured products
G. Components, packaging, labels and dietary supplements received	negligible	$23.9	Ensuring more consistently manufactured products
H. Master manufacturing record	negligible	negligible	Ensuring more consistently manufactured products
I. Batch production record	negligible	$3.7	Ensuring more consistently manufactured products
J. Laboratory operations	$0.1	negligible	Ensuring more consistently manufactured products
K. Manufacturing operations	negligible	$1.5	Preventing contamination and adulteration and ensuring more consistently manufactured products
L. Packaging and labeling operations	$0.1	$8.0	Ensuring more consistently manufactured products
M. Holding and distributing	$1.6	$0.3	Preventing contamination and adulteration and ensuring more consistently manufactured products

N. Returned dietary supplements	negligible	$0.2	Preventing contamination and adulteration and ensuring more consistently manufactured products
O. Product complaints	$0.1	$3.4	Preventing contamination and adulteration and ensuring more consistently manufactured products
P. Records and recordkeeping	not applicable	not applicable	not applicable

(Comment 359) We received several comments on the summary of the costs and benefits. In general, the comments state that we overestimated the benefits of the 2003 CGMP Proposal and underestimated the costs. Other comments assert that total estimated benefits of the 2003 CGMP Proposal would not be $216.6 million, as estimated by us, but as low as $13.9 million. Comments also estimate first year costs as high as $629 million, as opposed to our estimate of $54.5 million, with annual costs estimated as high as $860 million, as opposed to our estimate of $300.6 million. Other comments predict product prices will increase, and consumers will decrease consumption of dietary supplements.

(Response) We agree with the comments stating that we underestimated the costs and overestimated the quantified benefits of the 2003 CGMP Proposal. We have increased our estimate of costs in this final rule compared with the estimate in the 2003 CGMP Proposal. We have decreased our estimate of quantified benefits of the final rule compared with the estimate in the 2003 CGMP Proposal. As explained above, we are unable to quantify all of the benefits of the final rule. These changes in the estimated benefits and costs of this final rule reflect both the changes in the 2003 CGMP Proposal and the changes in our analysis in response to comments.

We agree with the comment that part of the costs of this final rule will be passed on to consumers as higher prices for dietary supplements. The annual costs of this final rule are about 1 percent of total spending on dietary supplements. We expect that the majority of these costs will be borne by consumers of dietary supplements, who will likely respond to the increase in prices by reducing consumption.

The comments suggesting very high costs and very low benefits did not persuade us that those extreme values were more likely than our estimates. We recognize, however, that the

uncertainties in our analysis make a broad range of benefits and costs possible. In the analysis of uncertainty we will show the range of predicted benefits and costs. We also will show the sensitivity of costs and benefits to certain key assumptions used in the analysis, and how changes in those assumptions can generate the extreme values cited in some comments.

9. Uncertainties in the Analysis

We used indirect measures of the benefits of this final rule which required several key assumptions that are critical for our estimates. With the exception of the recall benefit, which is based directly on our recall records, each component of the estimated benefits involves assumptions that reflect our uncertainty. The estimated costs also embody key assumptions, but the costs are less uncertain because of the greater availability of data on the components of cost.

One assumption that affects both estimated costs and estimated benefits is that manufacturing practices in the industry will persist in the absence of additional regulation. If the trend in the market is toward the adoption of more manufacturing controls than we are proposing here, then both the

costs and benefits of the rule will be less than we estimate. If the market trend is toward fewer voluntary controls, then both the costs and benefits of the regulation will be greater than we estimate.

The key assumptions in the benefits model are:

- There is an average of one reported illness for each recall. We assume that for each class 1 and 2 recalled product there was on average one illness that was reported to the public health authority.
- The frequency of actual illnesses is 100 times the frequency of reported illnesses. We recognize that the factor of 100, although it has empirical support, might be wrong and that there is likely to be considerable uncertainty about this estimate. The estimated health benefits will vary proportionally with the assumed multiplier. Direct health benefits double if we increase the factor multiplier from 100 to 200; lowering the multiplier to 50 halves the health benefits.
- In the baseline estimates, we used $5 million as the value of a statistical life and $300,000 as the value of a quality adjusted life year. The estimated health benefits change with changes in those valuations.

• We assume that the reported class 1 and 2 recalls that occurred from 1990 through 1999 represent the number and type of recalls that would have occurred in the future but for the implementation of this regulation. If the number or types of recalls are not representative, then we over or under estimated the benefit of avoiding recalls.

The costs of the rule chiefly depend on our assumptions about the amount and cost of additional testing. The amount of testing is highly uncertain; we have tried to model the number of tests based on number of ingredient shipments and the numbers and types of tests.

The key assumptions of the cost model are:

• Single shipment lots of ingredients and unlisted components will be used for many batches of final dietary supplement products. We assume that the average number of batches per incoming ingredient lot will be between 1 and 12, with 6.5 the most likely.

• All testing other than identity testing of incoming ingredients will be done on representative samples. The number of batches or lots tested will be the square root of n + 1, with n equal to the total number of batches or lots.

- The costs per test, which include the labor costs of selecting the samples and arranging for the tests, will be between $20 and $150, with $50 most likely.
- We assume that the survey results (Ref. E2) represent the best estimate available of current practices in the industry.

We first characterized the uncertainties as a probability distribution. We ran 5,000 computer simulations to estimate both benefits and costs. The simulations used distributions (given in the tables and the text) in place of point estimates.

Table 32. Distribution of Simulation Results for Annual Benefits and Costs

	5th Percentile	Mean	95th Percentile
Annual costs (in millions)	$90	$150	$260
Annual quantified benefits (in millions)	$24	$48	$79

The Monte Carlo computer simulations give the distributions of estimated benefits and costs. If the underlying distributions fully capture the uncertainty of the estimates, then the simulation results give a full picture of the uncertainty. With uncertain distributions used in the simulations, however, the ranges reported in the tables may not fully capture the uncertainties of the analysis. An alternative

way to show the uncertainty is to see how sensitive the results are to plausible changes in certain key assumptions. We start with benefits.

The reporting rate of illnesses associated with dietary supplements is unknown, which makes our estimate of the total number of illnesses highly uncertain. The uncertainty is compounded by the additional step of assuming an average of one reported illness per recall in our estimated baseline of reported illnesses. This assumption, however, is based on the fact that we do observe an average of about one reported illness per recall. We find much larger uncertainty in the likely number of total illnesses associated with reported illnesses. We use 1 percent as the average reporting rate, which implies that total illness are 100 times our estimate of reported illnesses. Although we believe that this reporting rate is the most plausible rate for illnesses associated with dietary supplements, the evidence supporting it is not strong. We show the effects of varying the rate.

Several comments questioned our assumption that the final rule will eliminate the recalls used to estimate benefits. We do not assume that all recalls will be eliminated, only that the

recalls identified above will be eliminated if the rule is fully effective. If the rule is not fully effective, then the quantified benefits will be less than we have estimated. In table 33 below we show the effects of different assumptions about the effectiveness of the final rule, along with the effects of different assumptions about the reporting rate. Our base assumptions are that the reporting rate is one percent (for a multiplier or 100) and the effectiveness of the final rule is 100 percent.

Table 33. Sensitivity of Quantified Benefits to Changes in Assumed Reporting rate and Effectiveness of the Final Rule (in millions)

Prevention Rate	Reporting Multiplier				
	1	*10*	*50*	*100*	*200*
20%	$0.7	$1.5	$5	$10	$18
40%	$1.4	$3	$10	$19	$37
60%	$2.2	$5	$15	$29	$55
80%	$2.9	$6	$20	$38	$74
100%	$3.6	$8	$25	**$48**	$92

In the economic analyses of recent regulations, we have used values of $5 million and $6.5 for a statistical life. Some estimates place the value of a statistical life at $3 million.

We have used values of $100,000, $300,000, and $500,000 for a quality adjusted life year. For our baseline estimated benefits of this final rule, we use a $5 million value for a statistical life and a $300,000 value for a quality adjusted life year. In the sensitivity analysis, we use values of $3 million for a statistical life and $100,000 for a quality adjusted life year to generate a "low" estimate of health benefits equal to $25 million, and values of $6.5 million and $500,000 to generate a "high" estimate equal to $66 million.

In the sensitivity analysis of costs, we change assumptions about the costs per test and amount of testing. We look at the sensitivity of changing assumptions about testing because it is the single largest contributor to annual costs; we estimate that annual testing costs will be about $60 million, about 40 percent of total costs. The second largest contributor to costs is paperwork, including written procedures and records. The annual cost of written procedures and record keeping for this final rule is about $17 million. The estimated costs of this final rule are not highly sensitive to the estimated costs of record keeping. Recordkeeping costs, and other costs as well (including testing costs) are driven by the number of batches

produced, our index of output. To show how changes in the estimated number of batches changes total costs, we include estimated costs for the 5th and 95th percentiles of batches produced, according to the survey of the industry.

Table 34. Sensitivity of Costs

Description	Estimated Annual Cost (after 3 years) (in millions)
Final rule	$150
1 batch of dietary supplements per shipment lot of an ingredient (baseline is 6.5)	$340
12 batches of dietary supplements per shipment lot of an ingredient (baseline is 6.5)	$116
Test 1 percent of batches or lots (baseline is square root of batches or lots plus 1)	$145
Test every batch or lot (baseline is square root of batches or lots plus 1)	$424
Average cost per test is $20 (baseline is $60)	$109
Average cost per test is $100 (baseline is $60)	$189
5th percentile number of batches (baseline is distribution of survey results)	$100
95th percentile number of batches (baseline is distribution of survey results)	$216

C. Initial Regulatory Flexibility Analysis

1. Introduction

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

2. Economic Effects on Small Entities

a. Number of small entities affected. The final rule will affect many small entities. A small business in this industry is any establishment with fewer than 500 employees. For purposes of the cost-benefit analysis, we also looked at the category we call very small establishments: Establishments with fewer than 20 employees. Based on the survey, we estimated that 774 establishments, 53 percent of the total establishments, could be classified as very small (under 20 employees) and 526 as small (20 to 499 employees), which is 36 percent of the total establishments. We estimated the total number of warehouses, wholesalers, and other holders likely to be covered by this regulation to be 15,689, of which 15,421 are small businesses.

The small establishments that will be affected by the final rule are those establishments that will have to perform the various required activities, and would not have done so without the rule. We determined estimated baseline (pre-CGMP requirements) manufacturing practices with the survey of the industry (Ref. E3). The survey asked representative respondents to answer a series of questions, including how many employees they had and what their existing practices were. From the survey, we determined that small establishments do not now follow all of the provisions of the final rule. Those that do not follow all the provisions will incur a cost to do so.

b. Costs to small entities. Implementation costs vary across establishments depending on current practices and the types of products manufactured, packaged, labeled, or held. We estimated the range of current practices using the survey of the industry. The cost model divided establishments by size, which allowed us to estimate the distribution of costs per establishment for each size and product class. Table 35 shows the cost per establishment for very small and small establishments. For comparison, we include the estimated average cost per large establishment and the median revenues for

each size category. As the table shows, costs per establishment are proportionally higher for very small than for large establishments. The table's most striking result is that annual costs are highest for small (20 to 499 employees) establishments.

Table 35. Costs per Establishment, by Size

	Set-up Costs per Establishment	Annual Costs per Establishment	Median Annual Revenue per Establishment
Very small establishments	$26,000	$37,000	Under $ 1 million
Small establishments	$19,000	$144,000	$5 to $10 million
Large establishments	$30,000	$60,000	$10 to $50 million
Warehouses, wholesalers, and other holders	$250	$950	Not applicable

Small establishments that do not perform a substantial number of the actions required by the final rule will bear relatively high costs for compliance with the provisions of this final rule. Although the final rule will raise product prices, the price increase (which would largely be determined by changes made by large establishments) may be much smaller than the increase in the average costs of very small producers. The average burden to very small establishments will be about 4 percent of annual revenue. The average burden to small

establishments will be 1.5 to 3 percent of annual revenue. Establishments with above average costs, and even establishments with average costs, could be hard pressed to continue to operate. Some of these may decide it is too costly and either change product lines or go out of business.

We use a model developed under contract by Eastern Research Group to estimate the effects of FDA regulations on small businesses (Ref. E25). The model is designed to assess the effects of a wide range of potential regulatory activities, ranging from HACCP to product labeling. CGMP regulations are included as a potential regulatory activity. The model allows us to predict the probability and frequency of small business failure as a result of our regulations.

We ran the model for the final rule. The model predicts that, as a result of the final rule, 140 very small, and 32 small dietary supplement manufacturers will probably go out of business. The model estimates the number of workers in those firms to be about 2,500.

The regulatory costs of this final rule will also discourage new small businesses from entering the industry. The dietary supplement has been characterized by substantial entry

of small businesses. Although we cannot quantify how much that will change, we expect that the rate of entry of very small and small businesses will decrease.

3. Regulatory Options

a. Exemptions for small entities. The burden on small establishments would be reduced if they were exempt from some provisions of the final rule. Most entities – we estimate close to 90 percent – affected by this final rule, however, are small. Exempting small establishments from some or all of its provisions would substantially reduce benefits.

b. Longer compliance periods. Lengthening the compliance period provides some regulatory relief for businesses with fewer than 500 employees. The longer compliance period will allow additional time for setting up recordkeeping, making capital improvements to the physical plant, purchasing new or replacement equipment, and other one-time expenditures. It will also delay the impact of the annual costs of compliance. We have given businesses with fewer than 20 employees an additional 24 months and businesses with fewer than 500 but more than 20 employees an additional 12 months for compliance. The final rule, then, will be phased-in over 36 months, with firms with

500 or more employees complying after 12 months, firms with under 500 but more than 20 employees after 24 months, and firms with fewer than 20 employees after 36 months. The cost savings of delay may well be larger than simply the present value of the delay because the firms with fewer than 500 employees may also be able to reduce their compliance costs by taking advantage of increases in industry knowledge and experience in implementing these regulations.

4. Description of Recordkeeping and Reporting

The Regulatory Flexibility Act requires a description of the recordkeeping and reporting required for compliance with this final rule. This final rule will require the preparation of records. As described in the Preliminary Regulatory Impact Analysis, written records or electronic documents must be kept that demonstrate that specific actions occurred in the manufacturing process in compliance with the final rule. Records that will be required in this final rule will demonstrate that corrective actions were taken; that equipment, instruments, and controls used in laboratory operations and quality control were installed and calibrated properly; that maintenance programs were followed; and that the results of any

testing show that components or dietary supplements meet the established specifications.

The compliance cost of recordkeeping is the sum of both the initial design and printing of the recordkeeping documents and the recurring costs of maintaining the records. The cost of training personnel to use the new documents is a recurring cost depending on how frequently documents are modified, how often personnel turn over, and how complicated the tasks are that are being recorded. The recurring costs are measured by the workers' wage rate multiplied by the expected labor hours necessary to for a written or electronic record and the time necessary for management to review the records to see that actions are documented accurately. In addition, electronic records necessitate recurring time spent ensuring that the equipment is serviced and maintained properly.

5. Summary

The final rule will have a significant economic impact on a substantial number of small entities.

(Comment 360) We received many comments on the Initial Regulatory Flexibility Analysis. Nearly all of the comments addressing small business state that the requirements of the

2003 CGMP Proposal, the testing requirements in particular, would be an enormous burden on small business. Other comments assert that, because of this burden, the rule is in violation of the Regulatory Flexibility Act. In addition, comments assert small business will be particularly burdened by the rule and that consumers will see little improvement in product safety as a result.

Some small firms estimate annual testing costs for the 2003 CGMP Proposal as high as $600,000, as opposed to the $60,000 per year estimated by us. Another firm estimates set-up costs in the range of 4 to 7 times our estimate and annual costs 8 to 30 times our estimate. Comments also express concern that we have underestimated the number of businesses forced to close if this rule is made final as proposed - one comment states that the rule would cause 50 percent of small businesses to shut down. Some comments assert that this rule is anti-competitive: that is, the comments claim that this rule will make dietary supplement manufacturing so expensive that only large companies will survive. In addition, a few comments note the loss of product choice, innovation, and domestic employment that accompany firm closures, in addition to the increase in prices

of products made by remaining firms. In addition, another comment suggests that foreign manufacturers will be at an advantage because they will not have to comply with the rule's requirements.

Some comments reiterate the points made earlier that the use of statistical sampling and supplier certificates of analysis could help reduce the burden on small business.

One comment states that it would be extremely costly for small firms to come into compliance with the 2003 CGMP Proposal, especially because, as several firms pointed out, small firms often produce batches that are small in size. A few comments, however, say that small firms should be made to comply with the new rule at the same time as large firms.

We received many comments on the compliance period of this rule. Some of these comments favor the extended compliance periods granted to small and very small firms. Other comments do not support the compliance periods, stating that they are not long enough for firms to set up recordkeeping systems, make capital improvements, and so on.

Other comments do not favor granting small firms more time to comply. Three comments state that granting small firms a

longer compliance period defeats the purpose of the rule, by making it difficult for consumers to determine which dietary supplements comply with the CGMPs and which do not yet comply. Another comment suggests that products made by firms not in compliance one year after the rule's effective date be labeled to say, "This product may not conform to government standards for purity and potency". Other comments propose a single compliance period for all firms.

(Response) We disagree with comments that the burden of this final rule violates the Regulatory Flexibility Act. The act requires agencies to consider the burden of their regulatory proposals on small entities, analyze and consider effective alternatives that reduce the burden on small entities, and make their analyses available for public comment. We have considered the burden of this final rule on all covered firms, including small businesses, and as a result have reduced certain testing requirements. In addition, small businesses are allowed more time to comply with the rule. The burden on small businesses remains large, but the Regulatory Flexibility Act does not require agencies to adopt regulations that impose the least burden on small entities. In addition, the Data Quality Act has

been fulfilled by using the most objective data available. In this analysis, we used data from surveys and from other Federal agencies. Although more data are desirable, we consider the quality of the data used in this analysis and in the references to be the best available and sufficient to fulfill the requirements of the Regulatory Flexibility and Data Quality Acts.

We have reduced the amount of testing required in this final rule in response to comments on the burden of testing costs on the 2003 CGMP Proposal.

We note that foreign firms that sell dietary supplements in the United States are required to be in compliance with the final rule.

In response to comments on the number of firms likely to go out of business, we have used our small business model to estimate that 172 small and very small firms will probably go out of business. Many other small firms – some of them already experiencing financial difficulties – will see their financial condition worsen as a result of this final rule.

We disagree with the comments that oppose longer compliance periods for small businesses. The additional time will only

slightly delay the full implementation (and full benefits) of this final rule, and may provide the margin of survival for some small businesses.

D. Unfunded Mandates

The Unfunded Mandates Reform Act of 1995 (Public Law 104-4) requires cost-benefit and other analyses for rules that would cost more than $100 million in a single year. The current inflation-adjusted statutory threshold is $115 million. This final rule qualifies as a significant rule under the statute. Most of the requirements of the Unfunded Mandates are fulfilled in the Executive Order 12866 analysis. The requirements under the Unfunded Mandates Reform Act of 1995 include assessing the rule's effects on future costs; productivity; particular regions, communities, or industrial sectors; economic growth; full employment; job creation; and exports.

The future costs from the rule are the recurring costs, which reach their long-term value in the third year after the 2003 CGMP Proposal would become final. These costs would be incurred by the establishments that manufacture, process, pack, label, transport, distribute, receive, hold, or import dietary ingredients or dietary products. Recurring costs from the

regulatory requirements will be incurred in each future year. Table 29, summarizes the annual future recurring costs.

The costs of the rule will be shared among manufacturers, processors, packagers, transporters, receivers, holders, and importers of dietary products, as well as domestic consumers. Much of the higher costs incurred by domestic suppliers of dietary supplement products as a result of these regulations will be passed on to consumers as higher prices. The higher prices will be offset by the benefits from these regulations.

Although this final regulation is significant, we do not expect it to substantially affect national productivity, growth, jobs, or full employment. The total costs will be small relative to the economy, and will be offset by benefits. The improved safety and quality of dietary supplements leads to less illness and fewer sick days taken by employees, and lower adjustment costs by firms that would otherwise need to hire replacement employees. Furthermore, the dietary supplement industry is too small a part of the domestic economy to influence overall economic activity. According to our model of small business effects, about 2,500 jobs may be lost in the

short run as a result of displaced workers in firms leaving the industry.

This final rule will require additional controls throughout the production and distribution chain for the manufacture of dietary supplements. The additional costs will increase the total costs of production and distribution for all of the regulated products, including products sold within the United States and across national borders. These increased costs will be partly passed on to consumers in the form of higher prices, which will tend to reduce the quantity demanded of the regulated products. The increased prices of U.S. exports could reduce the quantity of U.S. exports demanded, particularly in comparison with exports from countries that do not implement similar regulations. We expect this effect to be insignificant, because under the final rule the increases in the price of U.S. exports (and resulting decreases in quantity demanded) will be quite small.