

- 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. E2). We would only revise this estimate in light of new data of comparable quality to that provided by the survey.

(Comment 351) 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 to \$64,000.

(Response) The recordkeeping requirements in the final rule differ from the 2003 CGMP Proposal; revised estimates are included in this final regulatory impact analysis and paperwork reduction analysis.

(Comment 352) 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 businesses 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. E2). 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 note that the final rule does not require smooth and hard surfaces throughout the plant.

We estimated the capital costs as the costs of minor renovations to help meet sanitation requirements, not as the cost of, for example, 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 353) 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. We recognize, however, that it may be possible for a manufacturer to demonstrate, through various methods and processes in use over time for its particular operation, that a system of less than 100 percent identity testing would provide no material diminution of assurance of the identity of the dietary ingredient as compared to the assurance provided by 100-percent identity testing. To provide an opportunity for a manufacturer to make such a showing and reduce the frequency of identity testing of components that are dietary ingredients from 100 percent to some lower frequency, we decided to provide, in an interim final rule published elsewhere in this issue of the **Federal Register**, a procedure that allows for submission to, and review by, FDA of an alternative to the required 100-percent identity testing of components that are dietary ingredients, provided certain conditions are met.

(Comment 354) 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 355) 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 three to six. 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 vitamin 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 shipment lot of 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 dietary ingredient is used in six 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. E7). 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 dietary ingredients. Other dietary supplements, mainly herbals, contain about four listed dietary ingredients (Ref. E7).

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. E21) says that four to six 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 six for vitamins and minerals, and zero to four for herbal and other products.

Number of shipments (i.e., 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. E21), 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 on the number of batches produced per establishment (Ref. E2). 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. E22 and E23), 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. By assuming a single distribution for testing costs, we may overestimate testing costs for sectors or products with below-average costs and underestimate testing cost for sectors with above-average costs. In the cost model, for example, we distinguish between botanical ingredients and nonbotanical ingredients in the number of tests, but not in average testing costs. If the average cost of testing botanical products is higher than the average cost for vitamins and minerals, the distribution of costs may underestimate total testing costs for botanical products. We do not have sufficient information on the range of testing costs for botanical ingredients to determine if the average cost of testing is higher or lower than for other ingredients.

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, shown as follows, 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. E7)
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. E21
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. E2
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 and \$150; \$50 most likely; \$60 average	Refs. E22 and E23

(Comment 356) 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, Ph.D.-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 cost of \$26 per hour to estimate the cost of labor (Ref. E24). 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 most of the costs estimated as labor costs all involved ordinary labor tasks such as sanitation, monitoring, and recordkeeping. For more difficult or complicated tasks, more skilled workers may be required, but the overall average labor cost represents the best overall estimate for valuing the average cost of labor in the industry. 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) +
 (number of warehouses x costs per warehouse).

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 table

28 of this document 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	\$26	Employment Index, Bureau of Labor Statistics (Ref. E24)
Average size of establishments in square feet	very small = 24,674 small = 71,354 large = 596,000	Ref. E2
Average number of employees	very small = 7.6 small = 95 large = 1,005	Ref. E2
Procedures	8 to 16 hours setup time for small firms; 30 to 40 hours for large firms; annual cost is 10 percent of setup time per provision	Ref. E25
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. E26
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. E26
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. E2)
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. E2)
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 setup 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. E2)
Holding products and dietary ingredients: Capital requirements	Same as costs of equipment upgrades	Based on average sizes of establishments (Ref. E2)
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. E2)

The total setup costs for this final rule will be \$41 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 \$164 million, with the two largest costs being \$52 million for testing and \$24 million for records. The estimated total cost is the mean of a range of estimates based on the data and assumptions described in tables 27 and 28 of this document. In the uncertainty

and sensitivity analyses in section XXIV.B.11 of this document, 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 \$104 million to \$322 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 \$8 million to \$64 million, with a mean estimate of \$44 million. However, there are potentially large benefits of the rule that we were not able to quantify. The annual costs will be \$104 million to \$322 million, with a mean estimate of \$164 million. The rule will not be fully effective until 36 months after the publication date. Table 29 of this document shows how the phase-in of the final rule will generate the costs and quantifiable benefits for the first 4 years. Table 30 of this document shows the present and annualized values of costs and quantifiable 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, quantified and unquantified, of this final rule justify the costs.

TABLE 29.—COSTS AND QUANTIFIABLE BENEFITS BY YEAR

	1st year	2nd year	3rd year	4th year
Costs (in millions)	\$16	\$120	\$190	\$164
Benefits (in millions)	\$3	\$29	\$44	\$44

TABLE 30. PRESENT AND ANNUALIZED VALUES OF COSTS AND QUANTIFIABLE 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	\$2.3	\$1.6	\$153	\$149
Benefits	\$0.6	\$0.4	\$40	\$39

In table 31 of this document we show the annual costs for each subpart of the regulation. We identify selected costs for particular activities for some

of the subparts. 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.

TABLE 31.—COSTS BY SUBPART

Subpart	Setup Cost (in millions)	Annual Cost (in millions)
A. General provisions	not applicable	not applicable
B. Personnel	\$1.5	\$15.7
C. Physical plant and grounds	\$34.0	\$17.4
D. Equipment and utensils	\$0.9	\$2.3
E. Establish production and process control system	\$0.5	\$66.1
Subtotal for identity testing	negligible	\$45.0
Subtotal for all other testing	\$0.3	\$ 6.8
F. Quality control	negligible	\$2.1
G. Components, packaging, labels, and dietary supplements received	negligible	\$31.6
H. Master manufacturing record	\$0.1	negligible
I. Batch production record	negligible	\$5.4
J. Laboratory operations	\$0.2	negligible
K. Manufacturing operations	negligible	\$2.2
L. Packaging and labeling operations	\$0.1	\$10.8
M. Holding and distributing	\$2.7	\$0.5
N. Returned dietary supplements	negligible	\$0.2
O. Product complaints	\$0.1	\$4.5
P. Records and recordkeeping	not applicable	not applicable
Paperwork cost for all subparts	\$3.7	\$24.2

(Comment 357) 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, with annual costs estimated as high as \$860 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 previously, 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 less than 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. Benefits and Costs of Regulatory Options

We considered several regulatory options, including: (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. Although we received no comments on our analysis of the benefits and costs of options 2 through 6, we received many comments on the estimated benefits and costs of the 2003 CGMP Proposal. We have now revised the estimated quantifiable benefits and costs of the 2003 CGMP Proposal. The revised estimates are based on the comments received and the corrections made to the data.

Using the same method as used in this final rule to determine benefits, we estimate that the quantifiable benefits of the 2003 CGMP Proposal would be approximately the same as the quantifiable benefits of the final rule, \$44 million per year.

With the corrected estimated number of batches produced, we estimate that the setup costs of the 2003 CGMP Proposal would be \$51 million. If the 2003 CGMP Proposal had been finalized, the annual costs of complying with the requirements would be \$282 million, or about \$118 million more than this final rule. The 2003 CGMP Proposal relied more on testing final products and other controls closer to the end-product. Under the 2003 CGMP Proposal, for example, annual testing costs would be about \$97 million.

10. Cost Effectiveness Analysis

Both benefit-cost analysis and cost-effectiveness analysis provide a systematic framework for identifying and evaluating the likely outcomes of alternative regulatory choices. OMB Circular A-4 requires that major rulemakings be supported by both types of analysis wherever possible. A cost-effectiveness analysis is particularly useful when the primary benefits of the rulemaking are improved public health and safety.¹⁸ The main advantage of measures of effectiveness are that they account for a rule's impact on morbidity

¹⁸It should be noted that many of the benefits of this rule are quality benefits that are not quantified and will not be part of this analysis.

(nonfatal illness, injury, impairment, and quality of life) as well as premature death. The inclusion of morbidity effects is important because some illnesses (e.g., asthma) cause more instances of pain and suffering than they do premature death.

The primary benefits expected to result from this rulemaking are reduced numbers of acute and chronic illnesses and reduced number of recalls involving dietary supplement products. We were not able to quantify chronic illnesses that could be avoided as a result of this rulemaking. We were able to determine that we could avoid about \$40 million annually in costs of acute illnesses and \$4 million in avoided recalls as a result of improved dietary supplement manufacturing.

We can use the \$40 million annually in avoided acute illnesses costs to calculate a cost-effectiveness measure for this rule; \$40 million in reduced illness costs translates into 48,662 QALDs saved on an annual basis. Given that the annual costs of this final rule are expected to be \$164 million, the cost of each QALD saved is \$3,370. This is an overestimate of the cost of a QALD saved because we were unable to quantify the benefits of reduced chronic illness as a result of this rulemaking.

11. 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 that reflect our uncertainty.

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.

In addition to the general assumption about the effects of the rule, we rely on several key assumptions.

We assume there is an average of one reported illness for each class 1 and 2 recall.

The frequency of actual illnesses is 100 times the frequency of reported illnesses. We recognize that there is considerable uncertainty about the factor of 100.

For the baseline estimates, we assume \$5 million is the value of a statistical life and \$300,000 is the value of a quality-adjusted life year. The estimated health benefits change with changes in those valuations.

Finally, we assume that the reported recalls that occurred from 1990 through 1999 represent the number and type of recalls that would have occurred but for the implementation of this regulation. The cost model also relies on several key assumptions. We assume that single shipment lots of ingredients and unlisted components will be used for many batches of final dietary supplement products. We assume that 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.

We also assume that 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 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)	\$109	\$164	\$260
Annual quantified benefits (in millions)	\$36	\$44	\$54

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.

For our baseline estimated benefits of this final rule, we use a \$5 million value for a statistical life (VSL) 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 and values of \$7 million and \$500,000 to generate a “high” estimate.

The reporting rate of illnesses associated with dietary supplements is unknown, which makes our estimate of the total number of illnesses highly uncertain. We use 1 percent as the average reporting rate, which implies that

total illness are 100 times our estimate of reported illnesses. Although we assume this reporting rate is the most plausible for illnesses associated with dietary supplements, the evidence supporting it is not strong. We show the effects of reporting rates of 2.5 percent and 10 percent.

(Comment 358) Several comments questioned our assumption that the final rule will eliminate the recalls used to estimate benefits.

(Response) We do not assume that all recalls will be eliminated; we only assume that the recalls caused by manufacturing problems identified previously 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 the following discussion we show the effects of different assumptions about the effectiveness of the final rule.

The quantified benefits depend on the hazards found in recalled products between 1990 and 1999. The 69 recalls in 1998 dominate the estimate, accounting for 58 percent of class 1 and class 2 recalls, and 35 percent of all recalls for the decade. In this sensitivity analysis we estimate the effect of excluding 1998 from the data used to estimate average annual benefits. We also consider the effects of using the annual average number of recalls from 2000 through 2005 to estimate benefits.

TABLE 33.—SENSITIVITY OF BENEFITS

Description	Estimated Annual Benefits (after 3 years) (in millions)
Final rule	\$44
VSL = \$3 million and \$/QALY = \$100,000 (baselines are \$5 million and \$300,000)	\$24
VSL = \$7 million and \$/QALY = \$500,000 (baselines are \$5 million and \$300,000)	\$64
Each recall represents one illness, with reporting rate of 10 percent (baseline is 1 percent)	\$8
Each recall represents one illness, with reporting rate of 2.5 percent (baseline is 1 percent)	\$20
Final rule reduces manufacturing recalls by 80 percent (baseline is 100 percent)	\$35
Exclude 1998 recalls from estimate, so average annual number of manufacturing recalls is 14 (baseline is 19.5)	\$27
Average annual number of manufacturing recalls = 2000–2005 average, so average per year is 10 (baseline is 19.5)	\$26

In the sensitivity analysis of annual costs, we change assumptions about the numbers covered by the rule, the number of batches produced per establishment, the number of lots per batch, the average costs per test, and the rate of verification testing.

The number of establishments covered is uncertain because we based it on voluntary survey responses and other evidence from the 1990s. If the number of establishments has increased or decreased, or if our original data overstated or understated the correct number, then the estimated costs will be either too low or too high. We show the effects of different numbers for one arbitrarily lower number covered and one arbitrarily higher number covered.

The number of batches produced is our basic measure of output. Annual costs therefore vary directly with this measure and its components. We show how the costs depend on the number of batches by estimating costs for 50 percent less and 50 percent more batches than estimated from the survey.

The number of shipment lots and the cost per test determine identity testing costs, the single largest contributor to annual costs. We show how the costs vary if the average number of batches per lot is 1 or 12. We vary the average cost per test from \$20 to \$100.

TABLE 34.—SENSITIVITY OF COSTS

Description	Estimated Annual Cost (after 3 years) (in millions)
Final rule	\$164
Number of covered establishments is 1,300 (baseline is 1,460)	\$148
Number of covered establishments is 1,600 (baseline is 1,460)	\$178
Number of batches are 50 percent of baseline (baseline is 444, 2,436, and 1,164)	\$104
Number of batches are 150 percent of baseline (baseline is 444, 2,436, and 1,164)	\$224
1 batch of dietary supplements per shipment lot of a dietary ingredient (baseline is 6.5)	\$322
12 batches of dietary supplements per shipment lot of a dietary ingredient (baseline is 6.5)	\$136
Average cost per test is \$20 (baseline is \$60)	\$129
Average cost per test is \$100 (baseline is \$60)	\$197

We combine the results of the sensitivity analyses to generate overall ranges for benefits and costs. We estimate that, once it is fully implemented, the annual benefits, able to be quantified, from the final rule will be \$8 million to \$64 million; the annual costs will be \$104 million to \$322 million.

C. Final 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 (Ref. E2), 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. Based on the results of the survey (Ref. E2), 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. E2). 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 applicable 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, which we describe in detail in section XXIV.B.7 of this document, divided establishments by size, which allowed us to estimate the distribution of costs per establishment for each size and product class. Table 35 of this document 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 table 35 of this document 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

	Setup Costs per Establishment	Annual Costs per Establishment	Median Annual Revenue per Establishment
Very small establishments	\$26,000	\$46,000	Under \$1 million
Small establishments	\$20,000	\$184,000	\$5 to \$10 million
Large establishments	\$31,000	\$69,000	\$10 to \$50 million
Warehouses, wholesalers, and other holders	\$360	\$1,000	Not applicable

TABLE 36.—TOTAL COSTS BY ESTABLISHMENT SIZE

	Setup Costs	Percent of Total Setup Costs	Annual Costs	Percent of Total Annual Costs
Very small establishments	\$20 million	49 percent	\$38 million	23 percent
Small establishments	\$10 million	24 percent	\$98 million	60 percent
Large establishments	\$5 million	12 percent	\$11 million	7 percent
Warehouses, wholesalers, and other holders	\$6 million	15 percent	\$17 million	10 percent

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. E27). 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 be at risk of going out of business. The model estimates the number of workers in those firms to be about 2,250.

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 20 or more 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 20 or more 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.

c. *Reduced requirements in the final rule.* The modification of requirements in this final rule, compared with the 2003 CGMP Proposal, significantly reduce the costs borne by small businesses. We estimate the average setup costs under the 2003 CGMP Proposal to be \$25,000 for very small establishments and \$40,000 for small establishments. We estimate that the annual costs of the 2003 CGMP Proposal would be \$90,000 for very small establishments and \$300,000 for small establishments. The final rule therefore reduces annual costs for very small establishments to about half of the estimated costs of the proposed rule and reduces costs for very small establishments to about 60 percent of the estimated costs of the 2003 CGMP Proposal. Under the 2003 CGMP Proposal, 216 very small and 50 small businesses would be at risk of going out of business, over 50 percent more than under the final rule.

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 2003 CGMP Proposal, 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 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 359) We received many comments on the 2003 CGMP Proposal Preliminary 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 setup 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 1 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 modified certain requirements to reduce the costs of the final rule as compared with the 2003 CGMP Proposal. 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. As explained in Section XXIV.B.7 of this document, we underestimated costs in the proposed rule because of an error in a contractor's report. We have corrected the cost calculations, including estimated testing costs, for this final regulatory flexibility analysis.

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 be at risk of going out of business. Many other small firms—some of them already experiencing financial difficulties—may 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 (2005) inflation-adjusted statutory threshold is \$122 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 effective date of this rule. These costs would be incurred, directly or indirectly, by the establishments that manufacture, process, pack, label, transport, distribute, receive, hold, or import dietary supplements or ingredients. Recurring costs from the regulatory requirements will be incurred in each future year. Table 29 of this document summarizes the annual future recurring costs.

The costs, direct and indirect, of the rule will be shared among manufacturers, processors, packagers, transporters, receivers, holders, and importers of dietary supplements or ingredients, 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 dietary supplement industry is too small a part of the domestic economy to influence overall economic activity.

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.

XXV. Analysis of Environmental Impact

We have carefully considered the potential environmental effects of this action. We have concluded under 21 CFR 25.30(h) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

XXVI. Federalism

We have analyzed this final rule in accordance with the principles set forth in Executive Order 13132. We have determined that the final rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Furthermore, we did not receive any comments from States or their representative organizations regarding to our analysis of the proposed rule regarding the principles set forth in Executive Order 13132. Accordingly, we conclude that the final rule does not contain policies that have federalism implications as defined in the Executive order and, consequently, a federalism summary impact statement is not required.

XXVII. References

The following references have been placed on display in the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20857, and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday. (FDA has verified the Web

site addresses, but FDA is not responsible for any subsequent changes to the Web sites after this document publishes in the **Federal Register**.)

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List of Subjects in 21 CFR Part 111

Dietary foods, Drugs, Foods, Packaging and containers.

■ Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, FDA is amending 21 CFR chapter I by adding part 111 to read as follows:

PART 111—CURRENT GOOD MANUFACTURING PRACTICE IN MANUFACTURING, PACKAGING, LABELING, OR HOLDING OPERATIONS FOR DIETARY SUPPLEMENTS

Subpart A—General Provisions

Sec.

111.1 Who is subject to this part?

111.3 What definitions apply to this part?

111.5 Do other statutory provisions and regulations apply?

Subpart B—Personnel

- 111.8 What are the requirements under this subpart B for written procedures?
- 111.10 What requirements apply for preventing microbial contamination from sick or infected personnel and for hygienic practices?
- 111.12 What personnel qualification requirements apply?
- 111.13 What supervisor requirements apply?
- 111.14 Under this subpart B, what records must you make and keep?

Subpart C—Physical Plant and Grounds

- 111.15 What sanitation requirements apply to your physical plant and grounds?
- 111.16 What are the requirements under this subpart C for written procedures?
- 111.20 What design and construction requirements apply to your physical plant?
- 111.23 Under this subpart C, what records must you make and keep?

Subpart D—Equipment and Utensils

- 111.25 What are the requirements under this subpart D for written procedures?
- 111.27 What requirements apply to the equipment and utensils that you use?
- 111.30 What requirements apply to automated, mechanical, or electronic equipment?
- 111.35 Under this subpart D, what records must you make and keep?

Subpart E—Requirement to Establish a Production and Process Control System

- 111.55 What are the requirements to implement a production and process control system?
- 111.60 What are the design requirements for the production and process control system?
- 111.65 What are the requirements for quality control operations?
- 111.70 What specifications must you establish?
- 111.73 What is your responsibility for determining whether established specifications are met?
- 111.75 What must you do to determine whether specifications are met?
- 111.77 What must you do if established specifications are not met?

- 111.80 What representative samples must you collect?
- 111.83 What are the requirements for reserve samples?
- 111.87 Who conducts a material review and makes a disposition decision?
- 111.90 What requirements apply to treatments, in-process adjustments, and reprocessing when there is a deviation or unanticipated occurrence or when a specification established in accordance with § 111.70 is not met?
- 111.95 Under this subpart E, what records must you make and keep?

Subpart F—Production and Process Control System: Requirements for Quality

Control

- 111.103 What are the requirements under this subpart F for written procedures?
- 111.105 What must quality control personnel do?
- 111.110 What quality control operations are required for laboratory operations associated with the production and process control system?
- 111.113 What quality control operations are required for a material review and disposition decision?
- 111.117 What quality control operations are required for equipment, instruments, and controls?
- 111.120 What quality control operations are required for components, packaging, and labels before use in the manufacture of a dietary supplement?
- 111.123 What quality control operations are required for the master manufacturing record, the batch production record, and manufacturing operations?
- 111.127 What quality control operations are required for packaging and labeling operations?
- 111.130 What quality control operations are required for returned dietary supplements?
- 111.135 What quality control operations are required for product complaints?
- 111.140 Under this subpart F, what records must you make and keep?

Subpart G—Production and Process Control System: Requirements for Components, Packaging, and Labels and for Product That You Receive for Packaging or Labeling as a Dietary Supplement

- 111.153 What are the requirements under this subpart G for written procedures?
- 111.155 What requirements apply to components of dietary supplements?
- 111.160 What requirements apply to packaging and labels received?
- 111.165 What requirements apply to a product received for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier)?
- 111.170 What requirements apply to rejected components, packaging, and labels, and to rejected products that are received for packaging or labeling as a dietary supplement?
- 111.180 Under this subpart G, what records must you make and keep?

Subpart H—Production and Process Control System: Requirements for the Master Manufacturing Record

- 111.205 What is the requirement to establish a master manufacturing record?
- 111.210 What must the master manufacturing record include?

Subpart I—Production and Process Control System: Requirements for the Batch Production Record

- 111.255 What is the requirement to establish a batch production record?
- 111.260 What must the batch record include?

Subpart J—Production and Process Control System: Requirements for Laboratory Operations

- 111.303 What are the requirements under this subpart J for written procedures?
- 111.310 What are the requirements for the laboratory facilities that you use?
- 111.315 What are the requirements for laboratory control processes?
- 111.320 What requirements apply to laboratory methods for testing and examination?
- 111.325 Under this subpart J, what records must you make and keep?

Subpart K—Production and Process Control System: Requirements for Manufacturing Operations

- 111.353 What are the requirements under this subpart K for written procedures?
- 111.355 What are the design requirements for manufacturing operations?
- 111.360 What are the requirements for sanitation?
- 111.365 What precautions must you take to prevent contamination?
- 111.370 What requirements apply to rejected dietary supplements?
- 111.375 Under this subpart K, what records must you make and keep?

Subpart L—Production and Process Control System: Requirements for Packaging and Labeling Operations

- 111.403 What are the requirements under this subpart L for written procedures?
- 111.410 What requirements apply to packaging and labels?
- 111.415 What requirements apply to filling, assembling, packaging, labeling, and related operations?
- 111.420 What requirements apply to repackaging and relabeling?
- 111.425 What requirements apply to a packaged and labeled dietary supplement that is rejected for distribution?
- 111.430 Under this subpart L, what records must you make and keep?

Subpart M—Holding and Distributing

- 111.453 What are the requirements under this subpart M for written procedures?
- 111.455 What requirements apply to holding components, dietary supplements, packaging, and labels?
- 111.460 What requirements apply to holding in-process material?
- 111.465 What requirements apply to holding reserve samples of dietary supplements?
- 111.470 What requirements apply to distributing dietary supplements?
- 111.475 Under this subpart M, what records must you make and keep?

Subpart N—Returned Dietary Supplements

- 111.503 What are the requirements under this subpart N for written procedures?
- 111.510 What requirements apply when a returned dietary supplement is received?
- 111.515 When must a returned dietary supplement be destroyed, or otherwise suitably disposed of?
- 111.520 When may a returned dietary supplement be salvaged?
- 111.525 What requirements apply to a returned dietary supplement that quality control personnel approve for reprocessing?
- 111.530 When must an investigation be conducted of your manufacturing processes and other batches?
- 111.535 Under this subpart N, what records must you make and keep?

Subpart O—Product Complaints

- 111.553 What are the requirements under this subpart O for written procedures?
- 111.560 What requirements apply to the review and investigation of a product complaint?
- 111.570 Under this subpart O, what records must you make and keep?

Subpart P—Records and Recordkeeping

- 111.605 What requirements apply to the records that you make and keep?
- 111.610 What records must be made available to FDA?

Authority: 21 U.S.C. 321, 342, 343, 371, 374, 381, 393; 42 U.S.C. 264.

Subpart A—General Provisions**§ 111.1 Who is subject to this part?**

(a) Except as provided by paragraph (b) of this section, you are subject to this part if you manufacture, package, label, or hold a dietary supplement, including:

(1) A dietary supplement you manufacture but that is packaged or labeled by another person; and

(2) A dietary supplement imported or offered for import in any State or territory of the United States, the District of Columbia, or the Commonwealth of Puerto Rico.

(b) The requirements pertaining to holding dietary supplements do not apply to you if you are holding those dietary supplements at a retail establishment for the sole purpose of direct retail sale to individual consumers. A retail establishment does not include a warehouse or other storage facility for a retailer or a warehouse or other storage facility that sells directly to individual consumers.

§ 111.3 What definitions apply to this part?

The definitions and interpretations of terms in section 201 of the Federal Food, Drug, and Cosmetic Act (the act) apply to such terms when used in this part. For the purpose of this part, the following definitions also apply:

Actual yield means the quantity that is actually produced at any appropriate step of manufacture or packaging of a particular dietary supplement.

Batch means a specific quantity of a dietary supplement that is uniform, that is intended to meet specifications for identity, purity, strength, and composition, and that is produced during a specified time period according to a single manufacturing record during the same cycle of manufacture.

Batch number, lot number, or control number means any distinctive group of letters, numbers, or symbols, or any combination of them, from which the complete history of the manufacturing, packaging, labeling, and/or holding of a batch or lot of dietary supplements can be determined.

Component means any substance intended for use in the manufacture of a dietary supplement, including those that may not appear in the finished

batch of the dietary supplement. Component includes dietary ingredients (as described in section 201(ff) of the act) and other ingredients.

Contact surface means any surface that contacts a component or dietary supplement, and those surfaces from which drainage onto the component or dietary supplement, or onto surfaces that contact the component or dietary supplement, occurs during the normal course of operations. Examples of contact surfaces include containers, utensils, tables, contact surfaces of equipment, and packaging.

Ingredient means any substance that is used in the manufacture of a dietary supplement and that is intended to be present in the finished batch of the dietary supplement. An ingredient includes, but is not necessarily limited to, a dietary ingredient as defined in section 201(ff) of the act.

In-process material means any material that is fabricated, compounded, blended, ground, extracted, sifted, sterilized, derived by chemical reaction, or processed in any other way for use in the manufacture of a dietary supplement.

Lot means a batch, or a specific identified portion of a batch, that is uniform and that is intended to meet specifications for identity, purity, strength, and composition; or, in the case of a dietary supplement produced by continuous process, a specific identified amount produced in a specified unit of time or quantity in a manner that is uniform and that is intended to meet specifications for identity, purity, strength, and composition.

Microorganisms means yeasts, molds, bacteria, viruses, and other similar microscopic organisms having public health or sanitary concern. This definition includes species that:

- (1) May have public health significance;
- (2) May cause a component or dietary supplement to decompose;

(3) Indicate that the component or dietary supplement is contaminated with filth; or

(4) Otherwise may cause the component or dietary supplement to be adulterated.

Must is used to state a requirement.

Pest means any objectionable insect or other animal including birds, rodents, flies, mites, and larvae.

Physical plant means all or any part of a building or facility used for or in connection with manufacturing, packaging, labeling, or holding a dietary supplement.

Product complaint means any communication that contains any allegation, written, electronic, or oral, expressing concern, for any reason, with the quality of a dietary supplement, that could be related to current good manufacturing practice. Examples of product complaints are: Foul odor, off taste, illness or injury, disintegration time, color variation, tablet size or size variation, under-filled container, foreign material in a dietary supplement container, improper packaging, mislabeling, or dietary supplements that are superpotent, subpotent, or contain the wrong ingredient, or contain a drug or other contaminant (e.g., bacteria, pesticide, mycotoxin, glass, lead).

Quality means that the dietary supplement consistently meets the established specifications for identity, purity, strength, and composition, and limits on contaminants, and has been manufactured, packaged, labeled, and held under conditions to prevent adulteration under section 402(a)(1), (a)(2), (a)(3), and (a)(4) of the act.

Quality control means a planned and systematic operation or procedure for ensuring the quality of a dietary supplement.

Quality control personnel means any person, persons, or group, within or outside of your organization, who you designate to be responsible for your quality control operations.

Representative sample means a sample that consists of an adequate number of units that are drawn based on rational criteria, such as random sampling, and that are intended to ensure that the sample accurately portrays the material being sampled.

Reprocessing means using, in the manufacture of a dietary supplement, clean, uncontaminated components or dietary supplements that have been previously removed from manufacturing and that have been made suitable for use in the manufacture of a dietary supplement.

Reserve sample means a representative sample of product that is held for a designated period of time.

Sanitize means to adequately treat cleaned equipment, containers, utensils, or any other cleaned contact surface by a process that is effective in destroying vegetative cells of microorganisms of public health significance, and in substantially reducing numbers of other microorganisms, but without adversely affecting the product or its safety for the consumer.

Theoretical yield means the quantity that would be produced at any appropriate step of manufacture or packaging of a particular dietary supplement, based upon the quantity of components or packaging to be used, in the absence of any loss or error in actual production.

Water activity (a_w) is a measure of the free moisture in a component or dietary supplement and is the quotient of the water vapor pressure of the substance divided by the vapor pressure of pure water at the same temperature.

We means the U.S. Food and Drug Administration (FDA).

You means a person who manufactures, packages, labels, or holds dietary supplements.

§ 111.5 Do other statutory provisions and regulations apply?

In addition to this part, you must comply with other applicable statutory provisions and regulations under the act related to dietary supplements.

Subpart B—Personnel

§ 111.8 What are the requirements under this subpart B for written procedures?

You must establish and follow written procedures for fulfilling the requirements of this subpart.

§ 111.10 What requirements apply for preventing microbial contamination from sick or infected personnel and for hygienic practices?

(a) *Preventing microbial contamination.* You must take measures to exclude from any operations any person who might be a source of microbial contamination, due to a health condition, where such contamination may occur, of any material, including components, dietary supplements, and contact surfaces used in the manufacture, packaging, labeling, or holding of a dietary supplement. Such measures include the following:

(1) Excluding from working in any operations that may result in contamination any person who, by medical examination, the person's acknowledgement, or supervisory observation, is shown to have, or appears to have, an illness, infection, open lesion, or any other abnormal source of microbial contamination, that could result in microbial contamination of components, dietary supplements, or contact surfaces, until the health condition no longer exists; and

(2) Instructing your employees to notify their supervisor(s) if they have or if there is a reasonable possibility that they have a health condition

described in paragraph (a)(1) of this section that could result in microbial contamination of any components, dietary supplements, or any contact surface.

(b) *Hygienic practices.* If you work in an operation during which adulteration of the component, dietary supplement, or contact surface could occur, you must use hygienic practices to the extent necessary to protect against such contamination of components, dietary supplements, or contact surfaces. These hygienic practices include the following:

- (1) Wearing outer garments in a manner that protects against the contamination of components, dietary supplements, or any contact surface;
- (2) Maintaining adequate personal cleanliness;
- (3) Washing hands thoroughly (and sanitizing if necessary to protect against contamination with microorganisms) in an adequate hand-washing facility:
 - (i) Before starting work; and
 - (ii) At any time when the hands may have become soiled or contaminated;
- (4) Removing all unsecured jewelry and other objects that might fall into components, dietary supplements, equipment, or packaging, and removing hand jewelry that cannot be adequately sanitized during periods in which components or dietary supplements are manipulated by hand. If hand jewelry cannot be removed, it must be covered by material that is maintained in an intact, clean, and sanitary condition and that effectively protects against contamination of components, dietary supplements, or contact surfaces;
- (5) Maintaining gloves used in handling components or dietary supplements in an intact, clean, and sanitary condition. The gloves must be of an impermeable material;
- (6) Wearing, where appropriate, in an effective manner, hair nets, caps, beard covers, or other effective hair restraints;

(7) Not storing clothing or other personal belongings in areas where components, dietary supplements, or any contact surfaces are exposed or where contact surfaces are washed;

(8) Not eating food, chewing gum, drinking beverages, or using tobacco products in areas where components, dietary supplements, or any contact surfaces are exposed, or where contact surfaces are washed; and

(9) Taking any other precautions necessary to protect against the contamination of components, dietary supplements, or contact surfaces with microorganisms, filth, or any other extraneous materials, including perspiration, hair, cosmetics, tobacco, chemicals, and medicines applied to the skin.

§ 111.12 What personnel qualification requirements apply?

(a) You must have qualified employees who manufacture, package, label, or hold dietary supplements.

(b) You must identify who is responsible for your quality control operations. Each person who is identified to perform quality control operations must be qualified to do so and have distinct and separate responsibilities related to performing such operations from those responsibilities that the person otherwise has when not performing such operations.

(c) Each person engaged in manufacturing, packaging, labeling, or holding, or in performing any quality control operations, must have the education, training, or experience to perform the person's assigned functions.

§ 111.13 What supervisor requirements apply?

(a) You must assign qualified personnel to supervise the manufacturing, packaging, labeling, or holding of dietary supplements.

(b) Each supervisor whom you use must be qualified by education, training, or experience to supervise.

§ 111.14 Under this subpart B, what records must you make and keep?

(a) You must make and keep records required under this subpart B in accordance with subpart P of this part.

(b) You must make and keep the following records:

(1) Written procedures for fulfilling the requirements of this subpart B;

and

(2) Documentation of training, including the date of the training, the type of training, and the person(s) trained.

Subpart C—Physical Plant and Grounds**§ 111.15 What sanitation requirements apply to your physical plant and grounds?**

(a) *Grounds.* You must keep the grounds of your physical plant in a condition that protects against the contamination of components, dietary supplements, or contact surfaces. The methods for adequate ground maintenance include:

(1) Properly storing equipment, removing litter and waste, and cutting weeds or grass within the immediate vicinity of the physical plant so that it does not attract pests, harbor pests, or provide pests a place for breeding;

(2) Maintaining roads, yards, and parking lots so that they do not constitute a source of contamination in areas where components, dietary supplements, or contact surfaces are exposed;

(3) Adequately draining areas that may contribute to the contamination of components, dietary supplements, or contact surfaces by seepage, filth or any other extraneous materials, or by providing a breeding place for pests;

(4) Adequately operating systems for waste treatment and disposal so that they do not constitute a source of contamination in areas where components, dietary supplements, or contact surfaces are exposed; and

(5) If your plant grounds are bordered by grounds not under your control, and if those other grounds are not maintained in the manner described in this section, you must exercise care in the plant by inspection, extermination, or other means to exclude pests, dirt, and filth or any other extraneous materials that may be a source of contamination.

(b) *Physical plant facilities.* (1) You must maintain your physical plant in a clean and sanitary condition; and

(2) You must maintain your physical plant in repair sufficient to prevent components, dietary supplements, or contact surfaces from becoming contaminated.

(c) *Cleaning compounds, sanitizing agents, pesticides, and other toxic materials.* (1) You must use cleaning compounds and sanitizing agents that are free from microorganisms of public health significance and that are safe and adequate under the conditions of use.

(2) You must not use or hold toxic materials in a physical plant in which components, dietary supplements, or contact surfaces are manufactured or exposed, unless those materials are necessary as follows:

- (i) To maintain clean and sanitary conditions;
- (ii) For use in laboratory testing procedures;
- (iii) For maintaining or operating the physical plant or equipment; or
- (iv) For use in the plant's operations.

(3) You must identify and hold cleaning compounds, sanitizing agents, pesticides, pesticide chemicals, and other toxic materials in a manner that protects against contamination of components, dietary supplements, or contact surfaces.

(d) *Pest control.* (1) You must not allow animals or pests in any area of your physical plant. Guard or guide dogs are allowed in some areas of your

physical plant if the presence of the dogs will not result in contamination of components, dietary supplements, or contact surfaces;

(2) You must take effective measures to exclude pests from the physical plant and to protect against contamination of components, dietary supplements, and contact surfaces on the premises by pests; and

(3) You must not use insecticides, fumigants, fungicides, or rodenticides, unless you take precautions to protect against the contamination of components, dietary supplements, or contact surfaces.

(e) *Water supply.* (1) You must provide water that is safe and sanitary, at suitable temperatures, and under pressure as needed, for all uses where water does not become a component of the dietary supplement.

(2) Water that is used in a manner such that the water may become a component of the dietary supplement, e.g., when such water contacts components, dietary supplements, or any contact surface, must, at a minimum, comply with applicable Federal, State, and local requirements and not contaminate the dietary supplement.

(f) *Plumbing.* The plumbing in your physical plant must be of an adequate size and design and be adequately installed and maintained to:

(1) Carry sufficient amounts of water to required locations throughout the physical plant;

(2) Properly convey sewage and liquid disposable waste from your physical plant;

(3) Avoid being a source of contamination to components, dietary supplements, water supplies, or any contact surface, or creating an unsanitary condition;

(4) Provide adequate floor drainage in all areas where floors are subject to flooding-type cleaning or where normal operations release or discharge water or other liquid waste on the floor; and

(5) Not allow backflow from, or cross connection between, piping systems that discharge waste water or sewage and piping systems that carry water used for manufacturing dietary supplements, for cleaning contact surfaces, or for use in bathrooms or hand-washing facilities.

(g) *Sewage disposal.* You must dispose of sewage into an adequate sewage system or through other adequate means.

(h) *Bathrooms.* You must provide your employees with adequate, readily accessible bathrooms. The bathrooms must be kept clean and must not be a potential source of contamination to components, dietary supplements, or contact surfaces.

(i) *Hand-washing facilities.* You must provide hand-washing facilities that are designed to ensure that an employee's hands are not a source of contamination of components, dietary supplements, or any contact surface, by providing facilities that are adequate, convenient, and furnish running water at a suitable temperature.

(j) *Trash disposal.* You must convey, store, and dispose of trash to:

(1) Minimize the development of odors;

(2) Minimize the potential for the trash to attract, harbor, or become a breeding place for pests;

(3) Protect against contamination of components, dietary supplements, any contact surface, water supplies, and grounds surrounding your physical plant; and

(4) Control hazardous waste to prevent contamination of components, dietary supplements, and contact surfaces.

(k) *Sanitation supervisors.* You must assign one or more employees to supervise overall sanitation. Each of these supervisors must be qualified by education, training, or experience to develop and supervise sanitation procedures.

§ 111.16 What are the requirements under this subpart C for written procedures?

You must establish and follow written procedures for cleaning the physical plant and for pest control.

§ 111.20 What design and construction requirements apply to your physical plant?

Any physical plant you use in the manufacture, packaging, labeling, or holding of dietary supplements must:

(a) Be suitable in size, construction, and design to facilitate maintenance, cleaning, and sanitizing operations;

(b) Have adequate space for the orderly placement of equipment and holding of materials as is necessary for maintenance, cleaning, and sanitizing operations and to prevent contamination and mixups of components and dietary supplements during manufacturing, packaging, labeling, or holding;

(c) Permit the use of proper precautions to reduce the potential for mixups or contamination of components, dietary supplements, or contact surfaces, with microorganisms, chemicals, filth, or other extraneous material. Your physical plant must have, and you must use, separate or defined areas of adequate size or other control systems, such as computerized inventory controls or automated systems of separation, to prevent contamination and mixups of components and dietary supplements during the following operations:

(1) Receiving, identifying, holding, and withholding from use, components, dietary supplements, packaging, and labels that will be used in or during the manufacturing, packaging, labeling, or holding of dietary supplements;

(2) Separating, as necessary, components, dietary supplements, packaging, and labels that are to be used in manufacturing from components, dietary supplements, packaging, or labels that are awaiting material review and disposition decision, reprocessing, or are awaiting disposal after rejection;

(3) Separating the manufacturing, packaging, labeling, and holding of different product types including different types of dietary supplements and other foods, cosmetics, and pharmaceutical products;

(4) Performing laboratory analyses and holding laboratory supplies and samples;

(5) Cleaning and sanitizing contact surfaces;

(6) Packaging and label operations; and

(7) Holding components or dietary supplements.

(d) Be designed and constructed in a manner that prevents contamination of components, dietary supplements, or contact surfaces.

(1) The design and construction must include:

(i) Floors, walls, and ceilings that can be adequately cleaned and kept clean and in good repair;

(ii) Fixtures, ducts, and pipes that do not contaminate components, dietary supplements, or contact surfaces by dripping or other leakage, or condensate;

(iii) Adequate ventilation or environmental control equipment such as airflow systems, including filters, fans, and other air-blowing equipment, that minimize odors and vapors (including steam and noxious fumes) in areas

where they may contaminate components, dietary supplements, or contact surfaces;

(iv) Equipment that controls temperature and humidity, when such equipment is necessary to ensure the quality of the dietary supplement; and

(v) Aisles or working spaces between equipment and walls that are adequately unobstructed and of adequate width to permit all persons to perform their duties and to protect against contamination of components, dietary supplements, or contact surfaces with clothing or personal contact.

(2) When fans and other air-blowing equipment are used, such fans and equipment must be located and operated in a manner that minimizes the potential for microorganisms and particulate matter to contaminate components, dietary supplements, or contact surfaces;

(e) Provide adequate light in:

(1) All areas where components or dietary supplements are examined, processed, or held;

(2) All areas where contact surfaces are cleaned; and

(3) Hand-washing areas, dressing and locker rooms, and bathrooms.

(f) Use safety-type light bulbs, fixtures, skylights, or other glass or glass-like materials when the light bulbs, fixtures, skylights or other glass or glass-like materials are suspended over exposed components or dietary supplements in any step of preparation, unless your physical plant is otherwise constructed in a manner that will protect against contamination of components or dietary supplements in case of breakage of glass or glass-like materials.

(g) Provide effective protection against contamination of components and dietary supplements in bulk fermentation vessels, by, for example:

(1) Use of protective coverings;

(2) Placement in areas where you can eliminate harborages for pests over and around the vessels;

(3) Placement in areas where you can check regularly for pests, pest infestation, filth or any other extraneous materials; and

(4) Use of skimming equipment.

(h) Use adequate screening or other protection against pests, where necessary.

§ 111.23 Under this subpart C, what records must you make and keep?

(a) You must make and keep records required under this subpart C in accordance with subpart P of this part.

(b) You must make and keep records of the written procedures for cleaning the physical plant and for pest control.

(c) You must make and keep records that show that water, when used in a manner such that the water may become a component of the dietary supplement, meets the requirements of § 111.15(e)(2).

Subpart D—Equipment and Utensils

§ 111.25 What are the requirements under this subpart D for written procedures?

You must establish and follow written procedures for fulfilling the requirements of this subpart D, including written procedures for:

(a) Calibrating instruments and controls that you use in manufacturing or testing a component or dietary supplement;

(b) Calibrating, inspecting, and checking automated, mechanical, and electronic equipment; and

(c) Maintaining, cleaning, and sanitizing, as necessary, all equipment, utensils, and any other contact surfaces that are used to manufacture, package, label, or hold components or dietary supplements.

§ 111.27 What requirements apply to the equipment and utensils that you use?

(a) You must use equipment and utensils that are of appropriate design, construction, and workmanship to enable them to be suitable for their intended use and to be adequately cleaned and properly maintained.

(1) Equipment and utensils include the following:

(i) Equipment used to hold or convey;

(ii) Equipment used to measure;

(iii) Equipment using compressed air or gas;

(iv) Equipment used to carry out processes in closed pipes and vessels;

and

(v) Equipment used in automated, mechanical, or electronic systems.

(2) You must use equipment and utensils of appropriate design and construction so that use will not result in the contamination of components or dietary supplements with:

(i) Lubricants;

(ii) Fuel;

(iii) Coolants;

(iv) Metal or glass fragments;

(v) Filth or any other extraneous material;

(vi) Contaminated water; or

(vii) Any other contaminants.

(3) All equipment and utensils you use must be:

(i) Installed and maintained to facilitate cleaning the equipment, utensils, and all adjacent spaces;

(ii) Corrosion-resistant if the equipment or utensils contact components or dietary supplements;

(iii) Made of nontoxic materials;

(iv) Designed and constructed to withstand the environment in which they are used, the action of components or dietary supplements, and, if applicable, cleaning compounds and sanitizing agents; and

(v) Maintained to protect components and dietary supplements from being contaminated by any source.

(4) Equipment and utensils you use must have seams that are smoothly bonded or maintained to minimize accumulation of dirt, filth, organic material, particles of components or dietary supplements, or any other extraneous materials or contaminants.

(5) Each freezer, refrigerator, and other cold storage compartment you use to hold components or dietary supplements:

(i) Must be fitted with an indicating thermometer, temperature-measuring device, or temperature-recording device that indicates and records, or allows for recording by hand, the temperature accurately within the compartment; and

(ii) Must have an automated device for regulating temperature or an automated alarm system to indicate a significant temperature change in a manual operation.

(6) Instruments or controls used in the manufacturing, packaging, labeling, or holding of a dietary supplement, and instruments or controls that you use to measure, regulate, or record temperatures, hydrogen-ion concentration (pH), water activity, or other conditions, to control or prevent the growth of microorganisms or other contamination must be:

(i) Accurate and precise;

(ii) Adequately maintained; and

(iii) Adequate in number for their designated uses.

(7) Compressed air or other gases you introduce mechanically into or onto a component, dietary supplement, or contact surface or that you use to clean

any contact surface must be treated in such a way that the component, dietary supplement, or contact surface is not contaminated.

(b) You must calibrate instruments and controls you use in manufacturing or testing a component or dietary supplement. You must calibrate:

(1) Before first use;

(2) At the frequency specified in writing by the manufacturer of the instrument and control; or

(3) At routine intervals or as otherwise necessary to ensure the accuracy and precision of the instrument and control.

(c) You must repair or replace instruments or controls that cannot be adjusted to agree with the reference standard.

(d) You must maintain, clean, and sanitize, as necessary, all equipment, utensils, and any other contact surfaces used to manufacture, package, label, or hold components or dietary supplements.

(1) Equipment and utensils must be taken apart as necessary for thorough maintenance, cleaning, and sanitizing.

(2) You must ensure that all contact surfaces, used for manufacturing or holding low-moisture components or dietary supplements, are in a dry and sanitary condition when in use. When the surfaces are wet-cleaned, they must be sanitized, when necessary, and thoroughly dried before subsequent use.

(3) If you use wet processing during manufacturing, you must clean and sanitize all contact surfaces, as necessary, to protect against the introduction of microorganisms into components or dietary supplements. When cleaning and sanitizing is necessary, you must clean and sanitize all contact surfaces before use and after any interruption during which the contact surface may have become contaminated. If you use contact surfaces in a continuous production operation or in consecutive operations involving different batches

of the same dietary supplement, you must adequately clean and sanitize the contact surfaces, as necessary.

(4) You must clean surfaces that do not come into direct contact with components or dietary supplements as frequently as necessary to protect against contaminating components or dietary supplements.

(5) Single-service articles (such as utensils intended for one-time use, paper cups, and paper towels) must be:

(i) Stored in appropriate containers; and

(ii) Handled, dispensed, used, and disposed of in a manner that protects against contamination of components, dietary supplements, or any contact surface.

(6) Cleaning compounds and sanitizing agents must be adequate for their intended use and safe under their conditions of use;

(7) You must store cleaned and sanitized portable equipment and utensils that have contact surfaces in a location and manner that protects them from contamination.

§ 111.30 What requirements apply to automated, mechanical, or electronic equipment?

For any automated, mechanical, or electronic equipment that you use to manufacture, package, label, or hold a dietary supplement, you must:

(a) Design or select equipment to ensure that dietary supplement specifications are consistently met;

(b) Determine the suitability of the equipment by ensuring that your equipment is capable of operating satisfactorily within the operating limits required by the process;

(c) Routinely calibrate, inspect, or check the equipment to ensure proper performance. Your quality control personnel must periodically review these calibrations, inspections, or checks;

(d) Establish and use appropriate controls for automated, mechanical, and electronic equipment (including software for a computer controlled process) to ensure that any changes to the manufacturing, packaging, labeling, holding, or other operations are approved by quality control personnel and instituted only by authorized personnel; and

(e) Establish and use appropriate controls to ensure that the equipment functions in accordance with its intended use. These controls must be approved by quality control personnel.

§ 111.35 Under this subpart D, what records must you make and keep?

(a) You must make and keep records required under this subpart D in accordance with subpart P of this part.

(b) You must make and keep the following records:

(1) Written procedures for fulfilling the requirements of this subpart, including written procedures for:

(i) Calibrating instruments and controls that you use in manufacturing or testing a component or dietary supplement;

(ii) Calibrating, inspecting, and checking automated, mechanical, and electronic equipment; and

(iii) Maintaining, cleaning, and sanitizing, as necessary, all equipment, utensils, and any other contact surfaces that are used to manufacture, package, label, or hold components or dietary supplements;

(2) Documentation, in individual equipment logs, of the date of the use, maintenance, cleaning, and sanitizing of equipment, unless such documentation is kept with the batch record;

(3) Documentation of any calibration, each time the calibration is performed, for instruments and controls that you use in manufacturing or testing a component or dietary supplement. In your documentation, you must:

(i) Identify the instrument or control calibrated;

(ii) Provide the date of calibration;

(iii) Identify the reference standard used including the certification of accuracy of the known reference standard and a history of recertification of accuracy;

(iv) Identify the calibration method used, including appropriate limits for accuracy and precision of instruments and controls when calibrating;

(v) Provide the calibration reading or readings found;

(vi) Identify the recalibration method used, and reading or readings found, if accuracy or precision or both accuracy and precision limits for instruments and controls were not met; and

(vii) Include the initials of the person who performed the calibration and any recalibration.

(4) Written records of calibrations, inspections, and checks of automated, mechanical, and electronic equipment;

(5) Backup file(s) of current software programs (and of outdated software that is necessary to retrieve records that you are required to keep in accordance with subpart P of this part, when current software is not able to retrieve such records) and of data entered into computer systems that you use to manufacture, package, label, or hold dietary supplements.

(i) Your backup file (e.g., a hard copy of data you have entered, diskettes, tapes, microfilm, or compact disks) must be an exact and complete record of the data you entered.

(ii) You must keep your backup software programs and data secure from alterations, inadvertent erasures, or loss; and

(6) Documentation of the controls that you use to ensure that equipment functions in accordance with its intended use.

Subpart E—Requirement to Establish a Production and Process Control System

§ 111.55 What are the requirements to implement a production and process control system?

You must implement a system of production and process controls that covers all stages of manufacturing, packaging, labeling, and holding of the dietary supplement to ensure the quality of the dietary supplement and that the dietary supplement is packaged and labeled as specified in the master manufacturing record.

§ 111.60 What are the design requirements for the production and process control system?

(a) Your production and in-process control system must be designed to ensure that the dietary supplement is manufactured, packaged, labeled, and held in a manner that will ensure the quality of the dietary supplement and that the dietary supplement is packaged and labeled as specified in the master manufacturing record; and

(b) The production and in-process control system must include all requirements of subparts E through L of this part and must be reviewed and approved by quality control personnel.

§ 111.65 What are the requirements for quality control operations?

You must implement quality control operations in your manufacturing, packaging, labeling, and holding operations for producing the dietary supplement to ensure the quality of the dietary supplement and that the dietary

supplement is packaged and labeled as specified in the master manufacturing record.

§ 111.70 What specifications must you establish?

(a) You must establish a specification for any point, step, or stage in the manufacturing process where control is necessary to ensure the quality of the dietary supplement and that the dietary supplement is packaged and labeled as specified in the master manufacturing record.

(b) For each component that you use in the manufacture of a dietary supplement, you must establish component specifications as follows:

(1) You must establish an identity specification;

(2) You must establish component specifications that are necessary to ensure that specifications for the purity, strength and composition of dietary supplements manufactured using the components are met; and

(3) You must establish limits on those types of contamination that may adulterate or may lead to adulteration of the finished batch of the dietary supplement to ensure the quality of the dietary supplement.

(c) For the in-process production:

(1) You must establish in-process specifications for any point, step, or stage in the master manufacturing record where control is necessary to help ensure that specifications are met for the identity, purity, strength, and composition of the dietary supplements and, as necessary, for limits on those types of contamination that may adulterate or may lead to adulteration of the finished batch of the dietary supplement;

(2) You must provide adequate documentation of your basis for why meeting the in-process specifications, in combination with meeting component specifications, will help ensure that the specifications are met for the identity, purity, strength, and composition of the dietary supplements and for limits

on those types of contamination that may adulterate or may lead to adulteration of the finished batch of the dietary supplement; and

(3) Quality control personnel must review and approve the documentation that you provide under paragraph (c)(2) of this section.

(d) You must establish specifications for dietary supplement labels (label specifications) and for packaging that may come in contact with dietary supplements (packaging specifications). Packaging that may come into contact with dietary supplements must be safe and suitable for its intended use and must not be reactive or absorptive or otherwise affect the safety or quality of the dietary supplement.

(e) For each dietary supplement that you manufacture you must establish product specifications for the identity, purity, strength, and composition of the finished batch of the dietary supplement, and for limits on those types of contamination that may adulterate, or that may lead to adulteration of, the finished batch of the dietary supplement to ensure the quality of the dietary supplement.

(f) If you receive a product from a supplier for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier), you must establish specifications to provide sufficient assurance that the product you receive is adequately identified and is consistent with your purchase order.

(g) You must establish specifications for the packaging and labeling of the finished packaged and labeled dietary supplements, including specifications that ensure that you used the specified packaging and that you applied the specified label.

§ 111.73 What is your responsibility for determining whether established specifications are met?

You must determine whether the specifications you establish under § 111.70 are met.

§ 111.75 What must you do to determine whether specifications are met?

(a) Before you use a component, you must:

(1) Conduct at least one appropriate test or examination to verify the identity of any component that is a dietary ingredient; and

(2) Confirm the identity of other components and determine whether other applicable component specifications established in accordance with § 111.70(b) are met. To do so, you must either:

(i) Conduct appropriate tests or examinations; or

(ii) Rely on a certificate of analysis from the supplier of the component that you receive, provided that:

(A) You first qualify the supplier by establishing the reliability of the supplier's certificate of analysis through confirmation of the results of the supplier's tests or examinations;

(B) The certificate of analysis includes a description of the test or examination method(s) used, limits of the test or examinations, and actual results of the tests or examinations;

(C) You maintain documentation of how you qualified the supplier;

(D) You periodically re-confirm the supplier's certificate of analysis; and

(E) Your quality control personnel review and approve the documentation setting forth the basis for qualification (and re-qualification) of any supplier.

(b) You must monitor the in-process points, steps, or stages where control is necessary to ensure the quality of the finished batch of dietary supplement to:

(1) Determine whether the in-process specifications are met; and

(2) Detect any deviation or unanticipated occurrence that may result in a failure to meet specifications.

(c) For a subset of finished dietary supplement batches that you identify through a sound statistical sampling plan (or for every finished batch), you must verify that your finished batch of the dietary supplement meets product specifications for identity, purity, strength, composition, and for limits on those types of contamination that may adulterate or that may lead to adulteration of the finished batch of the dietary supplement. To do so:

(1) You must select one or more established specifications for identity, purity, strength, composition, and the limits on those types of contamination that may adulterate or that may lead to adulteration of the dietary supplement that, if tested or examined on the finished batches of the dietary supplement, would verify that the production and process control system is producing a dietary supplement that meets all product specifications (or only those product specifications not otherwise exempted from this provision by quality control personnel under paragraph (d) of this section);

(2) You must conduct appropriate tests or examinations to determine compliance with the specifications selected in paragraph (c)(1) of this section;

(3) You must provide adequate documentation of your basis for determining compliance with the specification(s) selected under paragraph (c)(1) of this section, through the use of appropriate tests or examinations conducted under paragraph (c)(2) of this section, will ensure that your finished batch of the dietary supplement meets all product specifications for identity, purity, strength, and composition, and the limits on those types of

contamination that may adulterate, or that may lead to the adulteration of, the dietary supplement; and

(4) Your quality control personnel must review and approve the documentation that you provide under paragraph (c)(3) of this section.

(d)(1) You may exempt one or more product specifications from verification requirements in paragraph (c)(1) of this section if you determine and document that the specifications you select under paragraph (c)(1) of this section for determination of compliance with specifications are not able to verify that the production and process control system is producing a dietary supplement that meets the exempted product specification and there is no scientifically valid method for testing or examining such exempted product specification at the finished batch stage. In such a case, you must document why, for example, any component and in-process testing, examination, or monitoring, and any other information, will ensure that such exempted product specification is met without verification through periodic testing of the finished batch; and

(2) Your quality control personnel must review and approve the documentation that you provide under paragraph (d)(1) of this section.

(e) Before you package or label a product that you receive for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier), you must visually examine the product and have documentation to determine whether the specifications that you established under § 111.70 (f) are met.

(f)(1) Before you use packaging, you must, at a minimum, conduct a visual identification of the containers and closures and review the supplier's invoice,

guarantee, or certification to determine whether the packaging specifications are met; and

(2) Before you use labels, you must, at a minimum, conduct a visual examination of the label and review the supplier's invoice, guarantee, or certification to determine whether label specifications are met.

(g) You must, at a minimum, conduct a visual examination of the packaging and labeling of the finished packaged and labeled dietary supplements to determine whether you used the specified packaging and applied the specified label.

(h)(1) You must ensure that the tests and examinations that you use to determine whether the specifications are met are appropriate, scientifically valid methods.

(2) The tests and examinations that you use must include at least one of the following:

- (i) Gross organoleptic analysis;
- (ii) Macroscopic analysis;
- (iii) Microscopic analysis;
- (iv) Chemical analysis; or
- (v) Other scientifically valid methods.

(i) You must establish corrective action plans for use when an established specification is not met.

§ 111.77 What must you do if established specifications are not met?

(a) For specifications established under § 111.70(a), (b)(2), (b)(3), (c), (d), (e), and (g) that you do not meet, quality control personnel, in accordance with the requirements in subpart F of this part, must reject the component, dietary supplement, package or label unless such personnel approve a treatment, an in-process adjustment, or reprocessing that will ensure the quality of the

finished dietary supplement and that the dietary supplement is packaged and labeled as specified in the master manufacturing record. No finished batch of dietary supplements may be released for distribution unless it complies with § 111.123(b).

(b) For specifications established under § 111.70(b)(1) that you do not meet, quality control personnel must reject the component and the component must not be used in manufacturing the dietary supplement.

(c) For specifications established under § 111.70(f) that you do not meet, quality control personnel must reject the product and the product may not be packaged or labeled for distribution as a dietary supplement.

§ 111.80 What representative samples must you collect?

The representative samples that you must collect include:

(a) Representative samples of each unique lot of components, packaging, and labels that you use to determine whether the components, packaging, and labels meet specifications established in accordance with § 111.70(b) and (d), and as applicable, § 111.70(a) (and, when you receive components, packaging, or labels from a supplier, representative samples of each unique shipment, and of each unique lot within each unique shipment);

(b) Representative samples of in-process materials for each manufactured batch at points, steps, or stages, in the manufacturing process as specified in the master manufacturing record where control is necessary to ensure the identity, purity, strength, and composition of dietary supplements to determine whether the in-process materials meet specifications established in accordance with § 111.70(c), and as applicable, § 111.70(a);

(c) Representative samples of a subset of finished batches of each dietary supplement that you manufacture, which you identify through a sound statistical sampling plan (or otherwise every finished batch), before releasing

for distribution to verify that the finished batch of dietary supplement meets product specifications established in accordance with § 111.70(e), and as applicable, § 111.70(a);

(d) Representative samples of each unique shipment, and of each unique lot within each unique shipment, of product that you receive for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier) to determine whether the received product meets specifications established in accordance with § 111.70(f), and as applicable, § 111.70(a); and

(e) Representative samples of each lot of packaged and labeled dietary supplements to determine whether the packaging and labeling of the finished packaged and labeled dietary supplements meet specifications established in accordance with § 111.70(g), and as applicable, § 111.70(a).

§ 111.83 What are the requirements for reserve samples?

(a) You must collect and hold reserve samples of each lot of packaged and labeled dietary supplements that you distribute.

(b) The reserve samples must:

(1) Be held using the same container-closure system in which the packaged and labeled dietary supplement is distributed, or if distributing dietary supplements to be packaged and labeled, using a container-closure system that provides essentially the same characteristics to protect against contamination or deterioration as the one in which it is distributed for packaging and labeling elsewhere;

(2) Be identified with the batch, lot, or control number;

(3) Be retained for 1 year past the shelf life date (if shelf life dating is used), or for 2 years from the date of distribution of the last batch of dietary supplements associated with the reserve sample, for use in appropriate investigations; and

(4) Consist of at least twice the quantity necessary for all tests or examinations to determine whether or not the dietary supplement meets product specifications.

§ 111.87 Who conducts a material review and makes a disposition decision?

Quality control personnel must conduct all required material reviews and make all required disposition decisions.

§ 111.90 What requirements apply to treatments, in-process adjustments, and reprocessing when there is a deviation or unanticipated occurrence or when a specification established in accordance with § 111.70 is not met?

(a) You must not reprocess a rejected dietary supplement or treat or provide an in-process adjustment to a component, packaging, or label to make it suitable for use in the manufacture of a dietary supplement unless:

(1) Quality control personnel conduct a material review and make a disposition decision to approve the reprocessing, treatment, or in-process adjustment; and

(2) The reprocessing, treatment, or in-process adjustment is permitted by § 111.77;

(b) You must not reprocess any dietary supplement or treat or provide an in-process adjustment to a component to make it suitable for use in the manufacture of a dietary supplement, unless:

(1) Quality control personnel conduct a material review and make a disposition decision that is based on a scientifically valid reason and approves the reprocessing, treatment, or in-process adjustment; and

(2) The reprocessing, treatment or in-process adjustment is permitted by § 111.77;

(c) Any batch of dietary supplement that is reprocessed, that contains components that you have treated, or to which you have made in-process

adjustments to make them suitable for use in the manufacture of the dietary supplement must be approved by quality control personnel and comply with § 111.123(b) before releasing for distribution.

§ 111.95 Under this subpart E, what records must you make and keep?

(a) You must make and keep records required under this subpart E in accordance with subpart P of this part.

(b) Under this subpart E, you must make and keep the following records:

(1) The specifications established;

(2) Documentation of your qualification of a supplier for the purpose of relying on the supplier's certificate of analysis;

(3) Documentation for why meeting in-process specifications, in combination with meeting component specifications, helps ensure that the dietary supplement meets the specifications for identity, purity, strength, and composition; and for limits on those types of contamination that may adulterate or may lead to adulteration of the finished batch of the dietary supplement; and

(4) Documentation for why the results of appropriate tests or examinations for the product specifications selected under § 111.75(c)(1) ensure that the dietary supplement meets all product specifications;

(5) Documentation for why any component and in-process testing, examination, or monitoring, and any other information, will ensure that a product specification that is exempted under § 111.75(d) is met without verification through periodic testing of the finished batch, including documentation that the selected specifications tested or examined under § 111.75 (c)(1) are not able to verify that the production and process control system is producing a dietary supplement that meets the exempted product

specification and there is no scientifically valid method for testing or examining such exempted product specification at the finished batch stage.

Subpart F—Production and Process Control System: Requirements for Quality Control

§ 111.103 What are the requirements under this subpart F for written procedures?

You must establish and follow written procedures for the responsibilities of the quality control operations, including written procedures for conducting a material review and making a disposition decision, and for approving or rejecting any reprocessing.

§ 111.105 What must quality control personnel do?

Quality control personnel must ensure that your manufacturing, packaging, labeling, and holding operations ensure the quality of the dietary supplement and that the dietary supplement is packaged and labeled as specified in the master manufacturing record. To do so, quality control personnel must perform operations that include:

(a) Approving or rejecting all processes, specifications, written procedures, controls, tests, and examinations, and deviations from or modifications to them, that may affect the identity, purity, strength, or composition of a dietary supplement;

(b) Reviewing and approving the documentation setting forth the basis for qualification of any supplier;

(c) Reviewing and approving the documentation setting forth the basis for why meeting in-process specifications, in combination with meeting component specifications, will help ensure that the identity, purity, strength, and composition of the dietary supplement are met;

(d) Reviewing and approving the documentation setting forth the basis for why the results of appropriate tests or examinations for each product specification selected under § 111.75(c)(1) will ensure that the finished batch of the dietary supplement meets product specifications;

(e) Reviewing and approving the basis and the documentation for why any product specification is exempted from the verification requirements in § 111.75(c)(1), and for why any component and in-process testing, examination, or monitoring, or other methods will ensure that such exempted product specification is met without verification through periodic testing of the finished batch;

(f) Ensuring that required representative samples are collected;

(g) Ensuring that required reserve samples are collected and held;

(h) Determining whether all specifications established under § 111.70(a) are met; and

(i) Performing other operations required under this subpart.

§ 111.110 What quality control operations are required for laboratory operations associated with the production and process control system?

Quality control operations for laboratory operations associated with the production and process control system must include:

(a) Reviewing and approving all laboratory control processes associated with the production and process control system;

(b) Ensuring that all tests and examinations required under § 111.75 are conducted; and

(c) Reviewing and approving the results of all tests and examinations required under § 111.75.

§ 111.113 What quality control operations are required for a material review and disposition decision?

(a) Quality control personnel must conduct a material review and make a disposition decision if:

(1) A specification established in accordance with § 111.70 is not met;

(2) A batch deviates from the master manufacturing record, including when any step established in the master manufacturing record is not completed and including any deviation from specifications;

(3) There is any unanticipated occurrence during the manufacturing operations that adulterates or may lead to adulteration of the component, dietary supplement, or packaging, or could lead to the use of a label not specified in the master manufacturing record;

(4) Calibration of an instrument or control suggests a problem that may have resulted in a failure to ensure the quality of a batch or batches of a dietary supplement; or

(5) A dietary supplement is returned.

(b)(1) When there is a deviation or unanticipated occurrence during the production and in-process control system that results in or could lead to adulteration of a component, dietary supplement, or packaging, or could lead to the use of a label not specified in the master manufacturing record, quality control personnel must reject the component, dietary supplement, packaging, or label unless it approves a treatment, an in-process adjustment, or reprocessing to correct the applicable deviation or occurrence.

(2) When a specification established in accordance with § 111.70 is not met, quality control personnel must reject the component, dietary supplement, package or label, unless quality control personnel approve a treatment, an in-process adjustment, or reprocessing, as permitted in § 111.77.

(c) The person who conducts a material review and makes the disposition decision must, at the time of performance, document that material review and disposition decision.

§ 111.117 What quality control operations are required for equipment, instruments, and controls?

Quality control operations for equipment, instruments, and controls must include:

(a) Reviewing and approving all processes for calibrating instruments and controls;

(b) Periodically reviewing all records for calibration of instruments and controls;

(c) Periodically reviewing all records for calibrations, inspections, and checks of automated, mechanical, or electronic equipment; and

(d) Reviewing and approving controls to ensure that automated, mechanical, or electronic equipment functions in accordance with its intended use.

§ 111.120 What quality control operations are required for components, packaging, and labels before use in the manufacture of a dietary supplement?

Quality control operations for components, packaging, and labels before use in the manufacture of a dietary supplement must include:

(a) Reviewing all receiving records for components, packaging, and labels;

(b) Determining whether all components, packaging, and labels conform to specifications established under § 111.70 (b) and (d);

(c) Conducting any required material review and making any required disposition decision;

(d) Approving or rejecting any treatment and in-process adjustments of components, packaging, or labels to make them suitable for use in the manufacture of a dietary supplement; and

(e) Approving, and releasing from quarantine, all components, packaging, and labels before they are used.

§ 111.123 What quality control operations are required for the master manufacturing record, the batch production record, and manufacturing operations?

(a) Quality control operations for the master manufacturing record, the batch production record, and manufacturing operations must include:

(1) Reviewing and approving all master manufacturing records and all modifications to the master manufacturing records;

(2) Reviewing and approving all batch production-related records;

(3) Reviewing all monitoring required under subpart E;

(4) Conducting any required material review and making any required disposition decision;

(5) Approving or rejecting any reprocessing;

(6) Determining whether all in-process specifications established in accordance with § 111.70(c) are met;

(7) Determining whether each finished batch conforms to product specifications established in accordance with § 111.70(e); and

(8) Approving and releasing, or rejecting, each finished batch for distribution, including any reprocessed finished batch.

(b) Quality control personnel must not approve and release for distribution:

(1) Any batch of dietary supplement for which any component in the batch does not meet its identity specification;

(2) Any batch of dietary supplement, including any reprocessed batch, that does not meet all product specifications established in accordance with § 111.70(e);

(3) Any batch of dietary supplement, including any reprocessed batch, that has not been manufactured, packaged, labeled, and held under conditions to prevent adulteration under section 402(a)(1), (a)(2), (a)(3), and (a)(4) of the act; and

(4) Any product received from a supplier for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier) for which sufficient assurance is not provided to adequately identify the product and to determine that the product is consistent with your purchase order.

§ 111.127 What quality control operations are required for packaging and labeling operations?

Quality control operations for packaging and labeling operations must include:

(a) Reviewing the results of any visual examination and documentation to ensure that specifications established under § 111.70(f) are met for all products that you receive for packaging and labeling as a dietary supplement (and for distribution rather than for return to the supplier);

(b) Approving, and releasing from quarantine, all products that you receive for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier) before they are used for packaging or labeling;

(c) Reviewing and approving all records for packaging and label operations;

(d) Determining whether the finished packaged and labeled dietary supplement conforms to specifications established in accordance with § 111.70(g);

(e) Conducting any required material review and making any required disposition decision;

(f) Approving or rejecting any repackaging of a packaged dietary supplement;

(g) Approving or rejecting any relabeling of a packaged and labeled dietary supplement; and

(h) Approving for release, or rejecting, any packaged and labeled dietary supplement (including a repackaged or relabeled dietary supplement) for distribution.

§ 111.130 What quality control operations are required for returned dietary supplements?

Quality control operations for returned dietary supplements must include:

(a) Conducting any required material review and making any required disposition decision; including:

(1) Determining whether tests or examination are necessary to determine compliance with product specifications established in accordance with § 111.70(e); and

(2) Reviewing the results of any tests or examinations that are conducted to determine compliance with product specifications established in accordance with § 111.70(e);

(b) Approving or rejecting any salvage and redistribution of any returned dietary supplement;

(c) Approving or rejecting any reprocessing of any returned dietary supplement; and

(d) Determining whether the reprocessed dietary supplement meets product specifications and either approving for release, or rejecting, any returned dietary supplement that is reprocessed.

§ 111.135 What quality control operations are required for product complaints?

Quality control operations for product complaints must include reviewing and approving decisions about whether to investigate a product complaint and reviewing and approving the findings and followup action of any investigation performed.

§ 111.140 Under this subpart F, what records must you make and keep?

(a) You must make and keep the records required under this subpart F in accordance with subpart P of this part.

(b) You must make and keep the following records:

(1) Written procedures for the responsibilities of the quality control operations, including written procedures for conducting a material review and making a disposition decision and written procedures for approving or rejecting any reprocessing;

(2) Written documentation, at the time of performance, that quality control personnel performed the review, approval, or rejection requirements by recording the following:

(i) Date that the review, approval, or rejection was performed; and

(ii) Signature of the person performing the review, approval, or rejection;

and

(3) Documentation of any material review and disposition decision and followup. Such documentation must be included in the appropriate batch production record and must include:

(i) Identification of the specific deviation or the unanticipated occurrence;

(ii) Description of your investigation into the cause of the deviation from the specification or the unanticipated occurrence;

(iii) Evaluation of whether or not the deviation or unanticipated occurrence has resulted in or could lead to a failure to ensure the quality of the dietary supplement or a failure to package and label the dietary supplement as specified in the master manufacturing record;

(iv) Identification of the action(s) taken to correct, and prevent a recurrence of, the deviation or the unanticipated occurrence;

(v) Explanation of what you did with the component, dietary supplement, packaging, or label;

(vi) A scientifically valid reason for any reprocessing of a dietary supplement that is rejected or any treatment or in-process adjustment of a component that is rejected; and

(vii) The signature of the individual(s) designated to perform the quality control operation, who conducted the material review and made the disposition decision, and of each qualified individual who provides information relevant to that material review and disposition decision.

Subpart G—Production and Process Control System: Requirements for Components, Packaging, and Labels and for Product That You Receive for Packaging or Labeling as a Dietary Supplement

§ 111.153 What are the requirements under this subpart G for written procedures?

You must establish and follow written procedures for fulfilling the requirements of this subpart G.

§ 111.155 What requirements apply to components of dietary supplements?

(a) You must visually examine each immediate container or grouping of immediate containers in a shipment that you receive for appropriate content

label, container damage, or broken seals to determine whether the container condition may have resulted in contamination or deterioration of the components;

(b) You must visually examine the supplier's invoice, guarantee, or certification in a shipment you receive to ensure the components are consistent with your purchase order;

(c) You must quarantine components before you use them in the manufacture of a dietary supplement until:

(1) You collect representative samples of each unique lot of components (and, for components that you receive, of each unique shipment, and of each unique lot within each unique shipment);

(2) Quality control personnel review and approve the results of any tests or examinations conducted on components; and

(3) Quality control personnel approve the components for use in the manufacture of a dietary supplement, including approval of any treatment (including in-process adjustments) of components to make them suitable for use in the manufacture of a dietary supplement, and releases them from quarantine.

(d)(1) You must identify each unique lot within each unique shipment of components that you receive and any lot of components that you produce in a manner that allows you to trace the lot to the supplier, the date received, the name of the component, the status of the component (e.g., quarantined, approved, or rejected); and to the dietary supplement that you manufactured and distributed.

(2) You must use this unique identifier whenever you record the disposition of each unique lot within each unique shipment of components that you receive and any lot of components that you produce.

(e) You must hold components under conditions that will protect against contamination and deterioration, and avoid mixups.

§ 111.160 What requirements apply to packaging and labels received?

(a) You must visually examine each immediate container or grouping of immediate containers in a shipment for appropriate content label, container damage, or broken seals to determine whether the container condition may have resulted in contamination or deterioration of the packaging and labels.

(b) You must visually examine the supplier's invoice, guarantee, or certification in a shipment to ensure that the packaging or labels are consistent with your purchase order.

(c) You must quarantine packaging and labels before you use them in the manufacture of a dietary supplement until:

(1) You collect representative samples of each unique shipment, and of each unique lot within each unique shipment, of packaging and labels and, at a minimum, conduct a visual identification of the immediate containers and closures;

(2) Quality control personnel review and approve the results of any tests or examinations conducted on the packaging and labels; and

(3) Quality control personnel approve the packaging and labels for use in the manufacture of a dietary supplement and release them from quarantine.

(d)(1) You must identify each unique lot within each unique shipment of packaging and labels in a manner that allows you to trace the lot to the supplier, the date received, the name of the packaging and label, the status

of the packaging and label (e.g., quarantined, approved, or rejected); and to the dietary supplement that you distributed; and

(2) You must use this unique identifier whenever you record the disposition of each unique lot within each unique shipment of packaging and labels.

(e) You must hold packaging and labels under conditions that will protect against contamination and deterioration, and avoid mixups.

§ 111.165 What requirements apply to a product received for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier)?

(a) You must visually examine each immediate container or grouping of immediate containers in a shipment of product that you receive for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier) for appropriate content label, container damage, or broken seals to determine whether the container condition may have resulted in contamination or deterioration of the received product.

(b) You must visually examine the supplier's invoice, guarantee, or certification in a shipment of the received product to ensure that the received product is consistent with your purchase order.

(c) You must quarantine the received product until:

(1) You collect representative samples of each unique shipment, and of each unique lot within each unique shipment, of received product;

(2) Quality control personnel review and approve the documentation to determine whether the received product meets the specifications that you established under § 111.70(f); and

(3) Quality control personnel approve the received product for packaging or labeling as a dietary supplement and release the received product from quarantine.

(d)(1) You must identify each unique lot within each unique shipment of received product in a manner that allows you to trace the lot to the supplier, the date received, the name of the received product, the status of the received product (e.g., quarantined, approved, or rejected), and to the product that you packaged or labeled and distributed as a dietary supplement.

(2) You must use this unique identifier whenever you record the disposition of each unique lot within each unique shipment of the received product.

(e) You must hold the received product under conditions that will protect against contamination and deterioration, and avoid mixups.

§ 111.170 What requirements apply to rejected components, packaging, and labels, and to rejected products that are received for packaging or labeling as a dietary supplement?

You must clearly identify, hold, and control under a quarantine system for appropriate disposition any component, packaging, and label, and any product that you receive for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier), that is rejected and unsuitable for use in manufacturing, packaging, or labeling operations.

§ 111.180 Under this subpart G, what records must you make and keep?

(a) You must make and keep records required under this subpart G in accordance with subpart P of this part.

(b) You must make and keep the following records:

(1) Written procedures for fulfilling the requirements of this subpart.

(2) Receiving records (including records such as certificates of analysis, suppliers' invoices, and suppliers' guarantees) for components, packaging, and labels and for products that you receive for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier); and

(3) Documentation that the requirements of this subpart were met.

(i) The person who performs the required operation must document, at the time of performance, that the required operation was performed.

(ii) The documentation must include:

(A) The date that the components, packaging, labels, or products that you receive for packaging or labeling as a dietary supplement were received;

(B) The initials of the person performing the required operation;

(C) The results of any tests or examinations conducted on components, packaging, or labels, and of any visual examination of product that you receive for packaging or labeling as a dietary supplement; and

(D) Any material review and disposition decision conducted on components, packaging, labels, or products that you receive for packaging or labeling as a dietary supplement.

Subpart H—Production and Process Control System: Requirements for the Master Manufacturing Record

§ 111.205 What is the requirement to establish a master manufacturing record?

(a) You must prepare and follow a written master manufacturing record for each unique formulation of dietary supplement that you manufacture, and for each batch size, to ensure uniformity in the finished batch from batch to batch.

(b) The master manufacturing record must:

(1) Identify specifications for the points, steps, or stages in the manufacturing process where control is necessary to ensure the quality of the

dietary supplement and that the dietary supplement is packaged and labeled as specified in the master manufacturing record; and

(2) Establish controls and procedures to ensure that each batch of dietary supplement that you manufacture meets the specifications identified in accordance with paragraph (b)(1) of this section.

(c) You must make and keep master manufacturing records in accordance with subpart P of this part.

§ 111.210 What must the master manufacturing record include?

The master manufacturing record must include:

(a) The name of the dietary supplement to be manufactured and the strength, concentration, weight, or measure of each dietary ingredient for each batch size;

(b) A complete list of components to be used;

(c) An accurate statement of the weight or measure of each component to be used;

(d) The identity and weight or measure of each dietary ingredient that will be declared on the Supplement Facts label and the identity of each ingredient that will be declared on the ingredients list of the dietary supplement;

(e) A statement of any intentional overage amount of a dietary ingredient;

(f) A statement of theoretical yield of a manufactured dietary supplement expected at each point, step, or stage of the manufacturing process where control is needed to ensure the quality of the dietary supplement, and the expected yield when you finish manufacturing the dietary supplement, including the maximum and minimum percentages of theoretical yield beyond which a deviation investigation of a batch is necessary and material review is conducted and disposition decision is made;

(g) A description of packaging and a representative label, or a cross-reference to the physical location of the actual or representative label;

(h) Written instructions, including the following:

(1) Specifications for each point, step, or stage in the manufacturing process where control is necessary to ensure the quality of the dietary supplement and that the dietary supplement is packaged and labeled as specified in the master manufacturing record;

(2) Procedures for sampling and a cross-reference to procedures for tests or examinations;

(3) Specific actions necessary to perform and verify points, steps, or stages in the manufacturing process where control is necessary to ensure the quality of the dietary supplement and that the dietary supplement is packaged and labeled as specified in the master manufacturing record.

(i) Such specific actions must include verifying the weight or measure of any component and verifying the addition of any component; and

(ii) For manual operations, such specific actions must include:

(A) One person weighing or measuring a component and another person verifying the weight or measure; and

(B) One person adding the component and another person verifying the addition.

(4) Special notations and precautions to be followed; and

(5) Corrective action plans for use when a specification is not met.

Subpart I—Production and Process Control System: Requirements for the Batch Production Record

§ 111.255 What is the requirement to establish a batch production record?

(a) You must prepare a batch production record every time you manufacture a batch of a dietary supplement;

(b) Your batch production record must include complete information relating to the production and control of each batch;

(c) Your batch production record must accurately follow the appropriate master manufacturing record and you must perform each step in the production of the batch; and

(d) You must make and keep batch production records in accordance with subpart P of this part.

§ 111.260 What must the batch record include?

The batch production record must include the following:

(a) The batch, lot, or control number:

(1) Of the finished batch of dietary supplement; and

(2) That you assign in accordance with § 111.415(f) for the following:

(i) Each lot of packaged and labeled dietary supplement from the finished batch of dietary supplement;

(ii) Each lot of dietary supplement, from the finished batch of dietary supplement, that you distribute to another person for packaging or labeling;

(b) The identity of equipment and processing lines used in producing the batch;

(c) The date and time of the maintenance, cleaning, and sanitizing of the equipment and processing lines used in producing the batch, or a cross-reference to records, such as individual equipment logs, where this information is retained;

(d) The unique identifier that you assigned to each component (or, when applicable, to a product that you receive from a supplier for packaging or labeling as a dietary supplement), packaging, and label used;

(e) The identity and weight or measure of each component used;

- (f) A statement of the actual yield and a statement of the percentage of theoretical yield at appropriate phases of processing;
- (g) The actual results obtained during any monitoring operation;
- (h) The results of any testing or examination performed during the batch production, or a cross-reference to such results;
- (i) Documentation that the finished dietary supplement meets specifications established in accordance with § 111.70(e) and (g);
- (j) Documentation, at the time of performance, of the manufacture of the batch, including:
- (1) The date on which each step of the master manufacturing record was performed; and
 - (2) The initials of the persons performing each step, including:
 - (i) The initials of the person responsible for weighing or measuring each component used in the batch;
 - (ii) The initials of the person responsible for verifying the weight or measure of each component used in the batch;
 - (iii) The initials of the person responsible for adding the component to the batch; and
 - (iv) The initials of the person responsible for verifying the addition of components to the batch;
- (k) Documentation, at the time of performance, of packaging and labeling operations, including:
- (1) The unique identifier that you assigned to packaging and labels used, the quantity of the packaging and labels used, and, when label reconciliation is required, reconciliation of any discrepancies between issuance and use of labels;

(2) An actual or representative label, or a cross-reference to the physical location of the actual or representative label specified in the master manufacturing record; and

(3) The results of any tests or examinations conducted on packaged and labeled dietary supplements (including repackaged or relabeled dietary supplements), or a cross-reference to the physical location of such results;

(l) Documentation at the time of performance that quality control personnel:

(1) Reviewed the batch production record, including:

(i) Review of any monitoring operation required under subpart E of this part; and

(ii) Review of the results of any tests and examinations, including tests and examinations conducted on components, in-process materials, finished batches of dietary supplements, and packaged and labeled dietary supplements;

(2) Approved or rejected any reprocessing or repackaging; and

(3) Approved and released, or rejected, the batch for distribution, including any reprocessed batch; and

(4) Approved and released, or rejected, the packaged and labeled dietary supplement, including any repackaged or relabeled dietary supplement.

(m) Documentation at the time of performance of any required material review and disposition decision.

(n) Documentation at the time of performance of any reprocessing.

Subpart J—Production and Process Control System: Requirements for Laboratory Operations

§ 111.303 What are the requirements under this subpart J for written procedures?

You must establish and follow written procedures for laboratory operations, including written procedures for the tests and examinations that you conduct to determine whether specifications are met.

§ 111.310 What are the requirements for the laboratory facilities that you use?

You must use adequate laboratory facilities to perform whatever testing and examinations are necessary to determine whether:

(a) Components that you use meet specifications;

(b) In-process specifications are met as specified in the master manufacturing record; and

(c) Dietary supplements that you manufacture meet specifications.

§ 111.315 What are the requirements for laboratory control processes?

You must establish and follow laboratory control processes that are reviewed and approved by quality control personnel, including the following:

(a) Use of criteria for establishing appropriate specifications;

(b) Use of sampling plans for obtaining representative samples, in accordance with subpart E of this part, of:

(1) Components, packaging, and labels;

(2) In-process materials;

(3) Finished batches of dietary supplements;

(4) Product that you receive for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier); and

(5) Packaged and labeled dietary supplements.