

store dietary supplements must conduct full product testing, then proposed § 111.70(b)(7) is unwarranted and unreasonable.

The comments assert that full product testing should not be required for companies that merely package, label, and store finished products. The comments assert that in-route contamination from the facility of a supplier or manufacturer to the facility of a packager, labeler, or distributor facility is unlikely to occur if the proper environmental conditions are maintained as required by other provisions of the 2003 CGMP Proposal. The comments assert that the responsibility for raw material and finished product testing should lie solely with the companies that handle the raw materials and dietary ingredients and that perform manufacturing duties. According to the comments, assuming the supplier/manufacturer complies with the final rule and adequately performs the required testing, reasonable cost/benefit analysis would dictate that redundant testing not be performed. Therefore, the comments assert that those who perform packaging and labeling operations should only be required to test those areas of contamination that are likely to occur during the shipment, or in the receipt, identification, packaging, and holding areas of production operations (e.g., surface contamination).

The comments state it is our duty to ensure that the industry is complying with any final rule, not the duty of certain segments of the industry to ensure that other segments of the industry are complying. Since in-route contamination is unlikely and rare, consumers would enjoy little or no benefit from redundant testing at a tremendous cost to the industry, particularly small businesses.

(Response) The term "specifications" in proposed § 111.70(b)(7) included any specifications that you established for packaged and labeled dietary

supplements under proposed § 111.35(e). In final § 111.415(g), we identify the specifications as those you establish in accordance with final § 111.70(g). In final § 111.70(g), we require you to establish specifications for the packaging and labeling for the finished packaged and labeled dietary supplements. We distinguish these specifications (final § 111.70(g)) from product specifications you must establish for a finished batch that you manufacture (final § 111.70(e)). The specifications that you establish and follow ensure that your product is what you establish in your master manufacturing record. As discussed in sections VI and section XII of this document, a master manufacturing record for a firm that only packages and labels the dietary supplement would include specifications that are applicable to its operations and would not include specifications related to, for example, components.

H. What Requirements Apply to Repackaging and Relabeling? (Final § 111.420)

1. Final § 111.420(a)

Final § 111.420(a) provides that you may repackaging or relabel dietary supplements only after your quality control personnel have approved such repackaging or relabeling. Final § 111.420(a) is similar to proposed § 111.70(d) with a restructuring of the provision for clarity. We did not receive comments specific to proposed § 111.70(d).

2. Final § 111.420(b) and (c)

Final § 111.420(b) requires you to examine a representative sample of each batch of repackaged or relabeled dietary supplements to determine whether the repackaged or relabeled dietary supplements meet all specifications established in accordance with § 111.70(g). Final § 111.420(c) requires that quality control personnel approve or reject each batch of repackaged or

re-labeled dietary supplement prior to its release for distribution. Final § 111.420(b) and (c) derive from proposed § 111.70(e) which would require you to retest or re-examine any repackaged or relabeled dietary supplements. Proposed § 111.70(e) also would require that any repackaged or relabeled dietary supplements meet all specifications and that the quality control unit approve or reject their release for distribution.

(Comment 305) Some comments assert that the proposed requirement that directs companies to retest or re-examine any repackaged or relabeled dietary supplement unnecessarily restricts the ability of the quality control unit to make an appropriate disposition decision. These comments assert that testing would not be necessary, for example, when a packager repackages a multiple vitamin softgel from a 500-count bottle to a 60-count bottle. The comments also assert that it would be costly to retest such product, and that such testing would not benefit consumer health and safety. The comments would revise proposed § 111.70(e) to give the quality control unit the authority to make an appropriate disposition decision, e.g., to assess the repackaged dietary supplement for conformity to specifications.

(Response) We agree that there are circumstances, such as those described by these comments, when testing would not be necessary. However, we disagree that it would not be necessary to “examine” a representative sample of the repackaged and relabeled dietary supplement to determine whether the required specifications are met, i.e., that you used the specified packaging and applied the specified label. If no examination of a representative sample took place, there would be no basis for the determination. We believe that final § 111.420(b) makes this clear.

I. What Requirements Apply to a Packaged and Labeled Dietary Supplement That Is Rejected for Distribution? (Final § 111.425)

Final § 111.425 requires you to clearly identify, hold, and control under a quarantine system for appropriate disposition any packaged and labeled dietary supplement that is rejected for distribution. Final § 111.425 derives from proposed § 111.74 which would require you to clearly identify, hold, and control under a quarantine system any component, dietary ingredient, dietary supplement, packaging, and label that is rejected and unsuitable for use in manufacturing, packaging, or label operations. Under the final rule, the requirements of proposed § 111.74 for components, packaging, and labels are being set forth in final § 111.170, and the requirements for a finished batch of dietary supplement are set forth in final § 111.370. Although the proposal did not include any packaged and labeled dietary supplement rejected for distribution, we are making this change to be consistent with the principle that rejected components, dietary supplements, packaging, or labels unsuitable for the distribution supply include finished product already packaged and labeled.

J. Under This Subpart, What Records Must You Make and Keep? (Final § 111.430)

1. Final § 111.430(a)

Final § 111.430(a) requires you to make and keep records required under this subpart in accordance with subpart P. Final § 111.430(a) derives from proposed § 111.70(h) with revisions associated with the reorganization. We did not receive comments specific to proposed § 111.70(h).

2. Final § 111.430(b)

As discussed in this section, final § 111.403 requires you to establish and follow written procedures for packaging and labeling operations. The written procedures are records. Therefore, final § 111.430(b) requires you to make and keep records of the written procedures for packaging and labeling operations.

XVIII. Comments on Holding and Distributing (Final Subpart M)*A. Organization of Final Subpart M*

In the 2003 CGMP Proposal, the requirements for holding operations were set forth in §§ 111.80, 111.82, and 111.83 in subpart F; the requirements for distribution operations were set forth in proposed § 111.90 in subpart F. As shown in table 14 of this document, the final rule moves the requirements related to holding and distributing operations to a new subpart (final Subpart M—Holding and Distributing). Table 14 lists the sections in the final rule and identifies the sections that form the basis of the final rule.

TABLE 14.—DERIVATION OF SECTIONS IN FINAL SUBPART M

Final Rule	2003 CGMP Proposal
§ 111.453 What are the requirements under this subpart M for written procedures?	N/A
§ 111.455 What requirements apply to holding components, dietary supplements, packaging, and labels?	§ 111.80
§ 111.460 What requirements apply to holding in-process material?	§ 111.82
§ 111.465 What requirements apply to holding reserve samples of dietary supplements?	§ 111.83(b)(1) and (b)(2)
§ 111.470 What requirements apply to distributing dietary supplements?	§ 111.90
§ 111.475 Under this subpart M, what records must you make and keep?	N/A

B. Highlights of Changes to the Proposed Requirements for Holding and Distributing

1. Revisions

The final rule includes changes that reflect that the scope of the final rule applies to persons who manufacture, package, label, or hold dietary supplements, unless subject to an exclusion in § 111.1.

2. Changes Associated With the Reorganization

Final § 111.465 in subpart M duplicates the requirement of final § 111.83(b)(3) to retain reserve samples of dietary supplements 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 samples. We are duplicating this requirement in this subpart because we believe that it will be useful to include the length of time that you must hold reserve samples in each place of the codified where it is logical to look for this information.

3. Changes After Considering Comments

The final rule:

- Does not require that you collect reserve samples of components;
- Provides flexibility as to the container-closure system used to hold reserve samples of dietary supplements;
- Includes a new requirement for written procedures; and
- Includes a new requirement to make and keep records of product distribution and written procedures.

C. General Comments on Proposed §§ 111.80, 111.82, 111.83, and 111.85

(Comment 306) One comment requests that factory sealed finished products, which have been specifically manufactured to be held and transported in a variety of conditions, be excluded from the requirements for holding. Another comment states that there are many types of companies or individuals in the supply chain who may “hold” a dietary supplement after final production, packaging, and labeling is complete. This comment seeks clarification that brokers, distributors, or wholesalers would be subject only to the proposed requirements for holding in proposed § 111.90.

(Response) If you hold a dietary supplement, you are subject to all applicable requirements of these CGMP regulations related to your operation. For example, if you are a wholesaler, you would be subject to the requirements in final § 111.470 for the dietary supplements you are holding for distribution as well as other applicable requirements, such as those related to personnel, physical plant and grounds, equipment and utensils, quality control, returned dietary supplements, and product complaints. We decline to list all of the requirements that would be applicable because individual operations may vary. However, we provide the following examples of requirements that would, or would not, apply in some specific circumstances. For example, if the dietary supplements that you hold require refrigeration, your refrigeration equipment must comply with the requirements to be fitted with an indicating thermometer, temperature-measuring device, or temperature-recording device that shows the temperature accurately within the compartment, and have an automated device for regulating temperature or an automatic alarm system to indicate a significant temperature change in a manual operation. However, you would not be required to establish specifications for the finished batch of the

dietary supplement, for product that is received for packaging or labeling, or for packaged and labeled dietary supplements or to determine whether such specifications are met if you only hold the product and do not perform any other functions.

*D. What Are the Requirements Under This Subpart for Written Procedures?
(Final § 111.453)*

We received many comments that recommended written procedures for various provisions. We address the need for written procedures generally in section IV of this document. We also respond to individual comments on specific provisions in the same section.

We are including a new provision, § 111.453 “What are the requirements under this subpart M for written procedures?” which requires you to establish and follow written procedures for holding and distribution operations.

E. What Requirements Apply to Holding Components, Dietary Supplements, Packaging, and Labels? (Final § 111.455)

1. Final § 111.455(a)

Final § 111.455(a) requires you to hold components and dietary supplements under appropriate conditions of temperature, humidity, and light so that the identity, purity, strength, and composition of the components and dietary supplements are not affected. Final § 111.455(a) derives from proposed § 111.80(a) which would require that you hold components, dietary ingredients, and dietary supplements under appropriate conditions of temperature, humidity, and light so that the identity, purity, quality, strength, and composition of the components, dietary ingredients, and dietary supplements are not affected.

We did not receive comments specific to proposed § 111.80(a).

2. Final § 111.455(b)

Final § 111.455(b) requires you to hold packaging and labels under appropriate conditions so that the packaging and labels are not adversely affected. Final § 111.455(b) derives from proposed § 111.80(b) with modifications for consistency with other provisions addressing packaging and labels.

We did not receive comments specific to proposed § 111.80(b).

3. Final § 111.455(c)

Final § 111.455(c) requires you to hold components, dietary supplements, packaging, and labels under conditions that do not lead to the mixup, contamination, or deterioration of components, dietary supplements, packaging, and labels. Final § 111.455(c) derives from proposed § 111.80(c).

We did not receive comments specific to proposed § 111.80(c).

F. What Requirements Apply to Holding In-Process Material? (Final § 111.460)

1. Final § 111.460(a)

Final § 111.460(a) requires you to identify and hold in-process material under conditions that protect against mixups, contamination, and deterioration. Final § 111.460(a) is similar to proposed § 111.82(a) with a grammatical change (i.e., a change from “that will protect them” to “that protect”).

We did not receive comments specific to proposed § 111.82(a).

2. Final § 111.460(b)

Final § 111.460(b) requires you to hold in-process material under appropriate conditions of temperature, humidity, and light. Final § 111.460(b) is identical to proposed § 111.82(b).

(Comment 307) One comment asserts it would be impractical, unnecessary, and extremely burdensome to maintain reserve samples of in-process materials. The comment asserts that collecting and holding samples of in-process materials would duplicate the requirement to collect and hold reserve samples of finished dietary supplements and require significant additional documentation, time, and storage space.

(Response) This comment may have misinterpreted proposed § 111.37(b)(11) (final §111.80(g)) which included requirements for collecting representative, rather than reserve, samples of in-process materials. The representative sample is used for those tests or examinations conducted to determine whether the batch meets specifications. A representative sample is held for only a short period of time, i.e., the time between the collection and the test or examination. Neither the 2003 CGMP Proposal nor this final rule includes a requirement to maintain a reserve sample of in-process materials.

G. Proposed Requirement for Holding Reserve Samples of Components

(Proposed § 111.83(a))

Proposed § 111.83(a) would require you to hold any collected reserve samples of components or dietary ingredients in a manner that protects against contamination and deterioration.

(Comment 308) One comment requests the final rule not require that manufacturers of dietary supplements collect and hold reserve samples of components. The comment asserts that all components can be traced back to

their source (i.e., the vendor or manufacturer of the material) for a more in-depth investigation if a dietary supplement comes under investigation due to a product complaint.

(Response) We agree with this comment. Therefore, the final rule contains no requirement for holding reserve samples of components, only finished dietary supplements, and, thus, proposed § 111.83(a) has no counterpart in the final rule.

H. What Requirements Apply to Holding Reserve Samples of Dietary Supplements? (Final § 111.465)

1. Final § 111.465(a)

Final § 111.465(a) requires you to hold reserve samples of dietary supplements in a manner that protects against contamination and deterioration. Under final § 111.465(a)(1) this includes holding the reserve sample under conditions consistent with product labels or, if no storage conditions are recommended on the label, under ordinary storage conditions. Final § 111.465(a)(1) derives from proposed § 111.83(b)(1) which would require you to hold reserve samples under conditions of use recommended or suggested in the label of the dietary supplement and, if no conditions of use are recommended or suggested in the label, then under ordinary conditions of use.

Final § 111.465(a)(1) refers to “conditions consistent with product labels” rather than to “conditions of use recommended or suggested in the label of the dietary supplement” and refers to “storage conditions” rather than “conditions of use.” This change is to reflect that the “conditions of use” referenced in the 2003 CGMP Proposal referred to the typical storage of the dietary supplement and not the consumption of the product by the consumer.

We did not receive comments specific to proposed § 111.83(b)(1).

Under final § 111.465(a)(2) the manner in which you hold reserve samples of dietary supplements includes 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 you distribute the dietary supplement for packaging and labeling elsewhere. Final § 111.465(a)(2) derives from proposed § 111.83(b)(2) which would require that the manner in which you hold reserve samples of dietary supplements include using the same container-closure system in which the dietary supplement is marketed or in one that provides the same level of protection against contamination or deterioration.

(Comment 309) One comment states a substantial amount of its product is shipped in bulk for packaging elsewhere. As a result, one often does not know the packaging being used to market the dietary supplement or how the packaged product is being stored. This comment recommends we revise the proposed regulation to require using the same container-closure system in which the dietary supplement is marketed “if known and if not in a typical market container-closure system.”

(Response) We acknowledge that some manufacturers of dietary supplements will distribute product in bulk and will not know the packaging used to market the dietary supplement. In addition, if you ship products in bulk, any commitment you make to your customer about the quality of the product you shipped would relate to the container you used to ship the bulk product. To address these points we provide in final § 111.465(a)(2) that you

have the flexibility to use 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. For example, if you distribute product in bulk using a polyethylene bottle that can hold 50 kilograms of the product, and there is an air space above the product, you would hold the reserve samples in a polyethylene bottle with an air space. However, you would use a bottle that is sized to fit the amount that you are holding in reserve.

2. Final § 111.465(b)

Final § 111.465(b) requires you to retain reserve samples 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 samples, for use in appropriate investigations. Final § 111.465(b) derives from proposed § 111.37(b)(12), which proposed, in part, that you must keep reserve samples for 3 years from the date of manufacture. Proposed § 111.37(b)(12) is now final § 111.83(b)(3) with a change to 2 years for the retention period and with changes that we are making consistent with comments that requested that the time frame for retaining reserve samples be linked to a shelf life date (or other form of expiration dating) when such a date is established. We discuss the reasons for the change from 3 years to 2 years and the change from “date of manufacture” to “the date of distribution” in section XXI of this document. In essence, final § 111.465(b) duplicates final § 111.83(b)(3) because we believe it will be useful to include the length of time you must hold reserve samples in each place in the codified where it is logical to look for this information.

I. What Requirements Apply to Distributing Dietary Supplements? (Final § 111.470)

Final § 111.470 requires you to distribute dietary supplements under conditions that will protect the dietary supplements against contamination and deterioration. Final § 111.470 derives from proposed § 111.90.

We did not receive comments specific to proposed § 111.90.

J. Under This Subpart, What Records Must You Make and Keep? (Final § 111.475)

In the 2003 CGMP Proposal, we invited comment on whether we should require you to make and keep records on the distribution of dietary supplements that you manufacture, package, or hold.

(Comment 310) Some comments assert that written records of product distribution would provide the ability to trace the shipment of each finished batch in the event of a product recall. One comment expresses the view that the ability to quickly and efficiently recall a product is an important safeguard in ensuring public health in the event of a serious problem. Another comment points out that the scope of recall would likely be much broader if records of product distribution were not available to pinpoint distribution.

(Response) We agree with these comments. Therefore, final § 111.475 requires you to make and keep records of product distribution in accordance with subpart P. In addition, we are adding a provision to complement final § 111.453 to ensure that records are maintained of the written procedures you establish for holding and distributing operations. As discussed, comments stressed that such procedures must be available to us during the course of an inspection.

(Comment 311) One comment asserts that the final rule should not include a requirement for records of product distribution, because such records are already common industry practice. This comment also points out that neither the food CGMPs in part 110 nor the agency's 1997 ANPRM have requirements for records of product distribution.

(Response) To the extent that the comment asserts that a practice that is a common industry practice should not be a requirement in the final rule, we disagree. CGMP includes those practices that may be commonly used in industry. In fact, the reason that such practices may be common in industry is because they are already considered to be CGMP. As we noted in the preamble to the 2003 CGMP Proposal (68 FR 12157 at 12221), however, not all dietary supplement establishments follow CGMP and, therefore, may not be keeping records of product distribution. Thus, in this final rule we do not exclude practices we consider to be CGMP and already may be used by some in industry.

The industry outline we published in the 1997 ANPR suggested (under Warehousing, Distribution, and Post-Distribution Procedures) that the CGMP rule require adequate distribution records to be maintained and retained for at least 1 year beyond the expected product shelf life, whereby an effective product recall can be achieved should one become necessary. Therefore, we disagree that the 1997 ANPRM did not suggest a requirement to make and retain records of product distribution.

XIX. Comments on Returned Dietary Supplements (Final Subpart N)

A. Organization of Final Subpart N

In the 2003 CGMP Proposal, the requirements for returned dietary supplements were set forth in proposed § 111.85. As shown in table 15 of this

document, we are reorganizing proposed § 111.85 into a distinct subpart (final Subpart N—Returned Dietary Supplements). Table 15 lists the sections in final subpart N and identifies the proposed sections that form the basis of the final rule.

TABLE 15.—DERIVATION OF SECTIONS IN FINAL SUBPART N

Final Rule	2003 CGMP Proposal
§ 111.503 What are the requirements under this subpart N for written procedures?	N/A
§ 111.510 What requirements apply when a returned dietary supplement is received?	§ 111.85(a)
§ 111.515 When must a returned dietary supplement be destroyed, or otherwise suitably disposed of?	§ 111.85(b) and (c)
§ 111.520 When may a returned dietary supplement be salvaged?	§ 111.37(b)(15)
§ 111.525 What requirements apply to a returned dietary supplement that quality control personnel approve for reprocessing?	§ 111.50(g)
§ 111.530 When must an investigation be conducted of your manufacturing processes and other batches?	§ 111.85(d)
§ 111.535 Under this subpart N, what records must you make and keep?	§ 111.50(g) § 111.85(e) and (f)

B. Highlights of Changes to the Proposed Requirements for Returned Dietary Supplements

1. Revisions

The final rule includes:

- Revisions that reflect that the final rule applies to persons who manufacture, package, label, or hold dietary supplements unless subject to an exclusion in § 111.1.
- A provision (final § 111.520) that we are adding for consistency, so that the final rule for returned dietary supplements clearly sets forth the

requirements for a positive outcome (i.e., when you may salvage a returned dietary supplement) as well as a negative outcome (i.e., when you must destroy or otherwise suitably dispose of a returned dietary supplement); and

- A provision (final § 111.525) we are adding for consistency, so that the final rule for returned dietary supplements clearly sets forth the requirements for reprocessed materials.

2. Changes After Considering Comments

The final rule:

- Includes a new requirement to establish and follow written procedures to fulfill the requirements for returned dietary supplements;

- Includes a revised description of the conditions that preclude you from salvaging a returned dietary supplement; and

- Provides flexibility for firms to salvage a returned dietary supplement without conducting tests to demonstrate that the dietary supplement meets all specifications, provided that quality control personnel conduct a material review and make a disposition decision to approve the salvage.

C. General Comments on Proposed § 111.85

(Comment 312) Several comments request we clarify the roles of the various parties in the “pre-consumer supply chain” for dietary supplements.

(Response) We have discussed, in section VI of this document, who is subject to the final rule in what the comment describes as the “pre-consumer supply chain” and do not repeat that discussion here. The requirements for returned dietary supplements do not distinguish between those returned to a person who manufactures a finished batch and those returned to a person whose role in the manufacturing process is limited to operations such as packaging, labeling, or holding.

Any reprocessing operations, other than repackaging or relabeling, by a packager or labeler who receives a product for packaging or labeling as a dietary supplement would make that packager or labeler subject to all relevant regulatory requirements under this final rule, as explained in section VI of this document. A packager or labeler that only conducts repackaging or relabeling operations may conclude that a product was returned for reasons related to a problem with the manufacture of the product it received for packaging or labeling, and therefore cannot be salvaged. In such a case, under final § 111.515 the packager or labeler would have to destroy or otherwise suitably dispose of the dietary supplement. Under final § 111.515, the packager or labeler may contact the manufacturer to determine if the packager or labeler could suitably dispose of the dietary supplement by sending it back to the manufacturer for possible reprocessing (see discussion of final § 111.515 in this section). A manufacturer who receives a dietary supplement returned by a packager or labeler would be required to comply with the requirements of final subpart N for returned dietary supplements, including requirements for any reprocessing of the returned dietary supplements.

D. What Are the Requirements Under This Subpart for Written Procedures?

(Final § 111.503)

We received many comments that recommended written procedures for various provisions. We address the need for written procedures generally in section IV of this document. We also respond to individual comments on specific provisions in the same section.

Final § 111.503 requires you to establish and follow written procedures to fulfill the requirements of subpart N. Under final § 111.535(b)(1) we are

requiring you to make and keep records of such written procedures. Such records would be available to us under the requirements in subpart P.

E. What Requirements Apply When a Returned Dietary Supplement is Received? (Final § 111.510)

Final § 111.510 requires you to identify and quarantine returned dietary supplements until quality control personnel conduct a material review and make a disposition decision. Final § 111.510 is similar to proposed § 111.85(a).

We did not receive comments specific to proposed § 111.85(a).

F. When Must a Returned Dietary Supplement Be Destroyed, or Otherwise Suitably Disposed Of? (Final § 111.515)

Final § 111.515(a) requires that you destroy, or otherwise suitably dispose of, any returned dietary supplement, unless the outcome of a material review and disposition decision is that quality control personnel either: (1) Approve the salvage of the returned dietary supplement for redistribution or (2) approve the returned dietary supplement for reprocessing. Final § 111.515(a) derives from the following proposed sections:

- Proposed § 111.85(b) which would require that you not salvage returned dietary supplements unless: (1) Evidence from their packaging (or, if possible, an inspection of the premises where the dietary ingredients and dietary supplements were held) indicates that the dietary ingredients and dietary supplements were not subjected to improper storage conditions and (2) tests demonstrate that the dietary ingredients or dietary supplements meet all specifications for identity, purity, quality, strength, and composition; and
- Proposed § 111.85(c) which would require that you destroy or suitably dispose of the returned dietary ingredients or dietary supplements if such dietary ingredients and dietary supplements do not meet specifications, unless

the quality control unit conducts a material review and makes a disposition decision to allow reprocessing.

Final § 111.515(a) includes editorial changes and other changes made after considering comments.

(Comment 313) Several comments assert it is unnecessary to conduct testing for all specifications for every returned product because products may be returned for reasons unrelated to product quality. For example, products may be returned due to overstocking, ordering the wrong quantity, going out of business, or failing to pay for the product on time. In addition, several comments assert that many returned products are intact, show no signs of mishandling, and are within the time limits for shelf life. These comments assert that a material review and disposition decision by the quality control unit to restock the material without retesting may be acceptable in these types of situations. Some comments assert that proposed § 111.85(b) is more restrictive than CGMP requirements for drug products, and suggest that testing need be conducted only when some doubt has been cast upon the identity, purity, quality, strength, or composition of the product, or if the product was returned for some other GMP-related problem.

Some comments contend that proposed §§ 111.35(i)(3)(v) and 111.85 would make it difficult to salvage any returned product because companies receiving returns often cannot verify the conditions under which such products were held. One comment refers to a stakeholder meeting when we indicated that the extent of testing requirements would depend upon the reason such products were returned. The comments state that the rule should allow flexibility as to when returned products must be tested.

Some comments specifically suggest the approach used in the USP (revised in 2nd supplement USP 26). These comments suggest that proposed § 111.85(b) be revised as follows: “If the conditions under which returned products have been held, stored, or shipped before or during their return, or if the condition of the product, its container, carton or labeling, as a result of storage or shipping, cast doubt on the safety, identity, strength, quality, or purity of the product, the returned product should be destroyed unless examination, testing or other investigations prove the product meets appropriate standards of safety, identity, strength, quality, or purity.”

These comments assert that inspection of the condition of the returned product could be used to determine that a product can be returned to inventory, and this inspection could be covered by internal procedures and based on experience in testing product stored under conditions that include extremes in heat and humidity without affecting the container or closure system.

(Response) As already discussed in this section, the final rule includes a new requirement that you establish and follow written procedures for handling returned dietary supplements. The final rule also retains the requirement that quality control personnel (formerly “unit” in the proposed rule) conduct a material review and make a disposition decision regarding all returned dietary supplements (see discussion of final § 111.113(a)(5) in section XI of this document). We agree with the comments that it is not necessary to conduct testing for all specifications for every returned product, because products may be returned for reasons unrelated to the quality of the dietary supplement. Final § 111.130 provides for quality control personnel to determine whether tests or examinations are necessary for returned dietary

supplements to determine compliance with product specifications. Therefore, final § 111.515 does not include a testing requirement. We believe the combination of written procedures and oversight by quality control personnel is adequate to determine the appropriate disposition of a returned dietary supplement, without requiring a test in every case to demonstrate that the dietary supplement meets specifications for identity, purity, strength, and composition.

In final § 111.515(a) we generally accept the comments' suggestions and reflect the approach of the USP for returned products. Thus, you must destroy or otherwise suitably dispose of the returned dietary supplement, unless the outcome of the material review and disposition decision is that quality control personnel approve the salvage of the returned dietary supplement for redistribution or approve the reprocessing of the returned dietary supplement. We provide flexibility on how quality control personnel may conduct a material review and make a disposition decision and do not require testing in every case. We respond in section V of this document to the comment asserting that the proposed CGMPs exceed the drug CGMPs.

G. When May a Returned Dietary Supplement Be Salvaged? (Final § 111.520)

Final § 111.520 permits the salvage of a returned dietary supplement only if quality control personnel conduct a material review and make a disposition decision to allow the salvage. Final § 111.520 is a conforming provision we are adding for consistency, so that the final requirement for returned dietary supplements clearly sets forth a positive outcome (i.e., when you may salvage a returned dietary supplement) as well as a negative outcome (i.e., when you must destroy or otherwise suitably dispose of a returned dietary supplement). Final § 111.520 is consistent with final § 111.130 (proposed § 111.37(b)(15))

which requires quality control personnel to approve the distribution of returned dietary supplements.

H. What Requirements Apply to a Returned Dietary Supplement That Quality Control Personnel Approve for Reprocessing? (Final § 111.525)

Final § 111.525(a) requires you to ensure that any returned dietary supplements that are reprocessed meet all product specifications established in accordance with final § 111.70(e). Final § 111.525(b) requires quality control personnel to approve or reject the release for distribution of any returned dietary supplement that is reprocessed. As with final § 111.520, final § 111.525 is a provision we are adding for consistency. Final § 111.525 is consistent with final § 111.90(c).

I. When Must an Investigation Be Conducted of Your Manufacturing Processes and Other Batches? (Final § 111.530)

Final § 111.530 requires that, if the reason for a dietary supplement being returned implicates other batches, you must conduct an investigation of your manufacturing processes and each of those other batches to determine compliance with specifications. Final § 111.530 derives from proposed § 111.85(d) which would require that if the reason for a dietary supplement being returned implicates associated batches, you must conduct an investigation of your manufacturing processes and those other batches to determine compliance with specifications. Final § 111.530 includes a nonsubstantive editorial change of “associated” to “each of those other batches” for clarity.

We did not receive comments specific to proposed § 111.85(d).

J. Under This Subpart, What Records Must You Make and Keep? (Final § 111.535)

Final § 111.535 sets forth the requirements to make and keep records for returned dietary supplements. Final § 111.180 derives from proposed § 111.85(e) and (f).

We did not receive comments specific to proposed § 111.85(e) or (f).

1. Final § 111.535(a)

Final § 111.535(a) requires you to make and keep records required under subpart N in accordance with subpart P. Final § 111.535(a) derives from proposed § 111.85(f) and includes changes associated with the reorganization.

2. Final § 111.535(b)(1)

As discussed in this section, the final rule includes a new requirement (final § 111.503) that you establish and follow written procedures to fulfill the requirements of subpart N. Those written procedures are records. Therefore, final § 111.535(b)(1) requires you to make and keep a record of the written procedures for fulfilling the requirements of subpart N.

3. Final § 111.535(b)(2)

Final § 111.535(b)(2) requires you to make and keep a record of any material review and disposition decision on a returned dietary supplement. Final § 111.535(b) derives from proposed § 111.85(e), with revisions associated with the reorganization.

4. Final § 111.535(b)(3)

Final § 111.535(b)(3) requires you to make and keep a record of the results of any testing or examination conducted to determine compliance with product specifications established under § 111.70(e). Final § 111.535(b) derives from

proposed § 111.85(e) which would require you to establish and keep records on any testing conducted to determine compliance with established specifications in the master manufacturing record for the type of dietary supplement that was returned. Final § 111.535(b)(3) includes the following revisions:

- Consistent with final § 111.70(e), final § 111.535(b)(3) substitutes “product specifications established under § 111.70(e)” for “established specifications in the master manufacturing record for the type of dietary ingredient or dietary supplement that was returned.”

- Consistent with final § 111.75(c), final § 111.535(b)(3) provides flexibility to use either tests or examinations to determine whether specifications are met.

5. Final § 111.535(b)(4)

Final § 111.535(b)(4) requires you to make and keep a record of documentation of the re-evaluation by quality control personnel of any dietary supplement that is reprocessed and the determination by quality control personnel of whether the reprocessed dietary supplement meets product specifications established in accordance with § 111.70(e). Final § 111.535(b)(4) is related to final § 111.525. Under final § 111.525, you must ensure that any returned dietary supplements that are reprocessed meet all product specifications you established under § 111.70(e) and quality control personnel must approve or reject the release for distribution of any returned dietary supplement that is reprocessed.

XX. Comments on Product Complaints (Final Subpart O)

A. Organization of Final Subpart O

In the 2003 CGMP Proposal, the requirements for consumer complaints were set forth in § 111.95. As shown in table 16 of this document, we are reorganizing proposed § 111.95 into three provisions in a new subpart (final Subpart O—Product Complaints). Table 16 lists the sections in final subpart O and identifies the provisions that form the basis for the final rule.

TABLE 16.—DERIVATION OF SECTIONS IN FINAL SUBPART O

Final Rule	2003 CGMP Proposal
§ 111.553 What are the requirements under this subpart O for written procedures?	N/A
§ 111.560 What requirements apply to the review and investigation of a product complaint?	§ 111.95(a), (b), (c), and (d)
§ 111.570 Under this subpart O, what records must you make and keep?	§ 111.95(e) and (f)

B. Highlights of Changes to the Proposed Requirements for Product Complaints

1. Revisions

The final rule:

- Includes changes that reflect the final rule applies to persons who manufacture, package, label, or hold dietary supplements unless subject to an exclusion in § 111.1.

- Uses the term “product complaint” rather than “consumer complaint,” and the definition of “product complaint” does not include an explanation about the types of complaints that may or may not be covered by the CGMP regulations. The definition does, however, include examples of product complaints.

2. Changes After Considering Comments

The final rule modifies the process for handling product complaints as follows:

- A qualified person investigates any product complaint that involves a possible failure of a dietary supplement to meet any requirements of part 111, without an intermediate step of having quality control personnel first determine whether the complaint should be investigated;
- Quality control personnel review and approve all decisions made by a qualified person about whether to investigate a product complaint and the findings and followup action of any investigation performed rather than conduct the investigation and followup; and
- The review and investigation of the product complaint extends to all relevant batches and records, without identifying specific records, and specific batches, that must be included in the review and investigation.

C. General Comments on Proposed § 111.95 (Final Subpart O)

(Comment 314) Some comments express general support for the proposed procedures for consumer complaints. Other comments request proposed § 111.95 be deleted. Most of these comments point out that we had announced the development of CFSAN's Adverse Event Reporting System (CAERS) for reporting to FDA adverse events attributed to food products and suggest that this new system would be the appropriate mechanism for handling complaints about dietary supplements.

(Response) We disagree with these comments. Because the problem giving rise to the complaint may be associated with a failure in manufacturing, packaging, labeling, or holding, it is CGMP for a firm that receives a product complaint to review it and investigate, if necessary, regardless of whether we

are notified about the complaint. An important goal of the firm's review and investigation is to determine whether there is a problem with the production and process control system for the manufacture, packaging, labeling, or holding of the dietary supplement. That goal would not be achieved merely by notifying us. A firm subject to any of the requirements of this final rule, whether such firm is a manufacturer, packager, labeler, or holder, is responsible for the requirements in subpart O for a product complaint it receives.

(Comment 315) Some comments assert that the proposed requirements for consumer complaints do not go far enough and urge that any final rule require any complaints that involve an adverse event be referred to us. The comments stress accurate reporting of adverse events is essential to long term evaluations of a product's safety.

(Response) Mandatory reporting requirements to us regarding adverse events related to dietary supplements are outside the scope of this rulemaking. This final rule addresses the internal processes and controls that persons who manufacture, package, label, or hold dietary supplements must follow. Mandatory reporting to FDA of serious adverse events, however, is now required as a result of the enactment of the "Dietary Supplement and Non-Prescription Drug Consumer Protection Act" (Public Law 109-462) signed into law on December 22, 2006. The new law requires manufacturers, packers, or distributors of such products to submit reports to FDA about serious adverse events involving such products based on specific information that they receive from the public. Serious adverse events are defined in the law as those events that result in death, a life-threatening situation, an inpatient hospitalization, a persistent or significant disability or incapacity, or a congenital anomaly or

birth defect or one that requires medical or surgical intervention to prevent such serious outcomes (based on reasonable medical judgment).

As discussed in the preamble to the 2003 CGMP Proposal (68 FR 12157 at 12217), however, we continue to strongly recommend that firms that receive product complaints, that are not “serious adverse events,” notify us about any illness or injury, because, for example, we may have additional expertise or data that may be helpful in investigating the complaint or determining whether the problem applies to more than one product. In light of the requirement in the final rule to establish and follow written procedures for handling product complaints, we encourage you to include our recommendations in the written procedures that you develop for handling product complaints (see discussion of final § 111.553 in this section).

(Comment 316) Some comments raise questions about who would be subject to the proposed requirements regarding consumer complaints. Some comments state the section should apply only to manufacturers of dietary supplements, not to manufacturers of dietary ingredients. Other comments are concerned that distributors who merely put their label on the finished product may be held responsible for keeping records of adverse events caused by failures to follow CGMPs during the manufacture of the supplements.

(Response) The final rule only applies to persons who manufacture, package, label, or hold a dietary supplement. We discuss the scope of this final rule in detail in section VI of this document.

In most cases, the person who receives a product complaint from a consumer will be the manufacturer, packager, or distributor of the dietary supplement. A distributor (also a “holder” under this final rule) who receives a product complaint must review and investigate that complaint to determine

whether the complaint relates to a failure of the processes under the control of the distributor, such as conditions of temperature, humidity, and light that could affect the identity, purity, strength, or composition of the dietary supplement. If the distributor concludes the problem is unrelated to any process under the control of the distributor, the distributor should contact the manufacturer. Under the final rule, any person in the manufacturing chain who receives a product complaint—regardless of the source—must comply with the requirements in this subpart O.

(Comment 317) One comment suggests proposed § 111.95, which describes requirements for consumer complaints, could be combined with proposed § 111.85 which describes requirements for returned dietary supplements.

(Response) We decline to adopt this suggestion. In this final rule, we are incorporating the requirements for returned dietary supplements into a distinct subpart (final subpart N) that sets forth requirements for returned dietary supplements. The procedures described in final subpart O, which relate solely to the handling of product complaints rather than returned dietary supplement products, are quite different from those described in final subpart N, which addresses the handling, review, and possible reprocessing of returned product.

(Comment 318) Some comments assert the proposed requirements for complaints are different from those for food CGMPs.

(Response) We are making no changes to the requirements after considering these comments. We responded in section V of this document to similar comments asserting that certain aspects of the proposed regulations are different from those for other food CGMP requirements.

D. What Are the Requirements Under This Subpart for Written Procedures?

(Final § 111.553)

We received many comments which recommended written procedures for various provisions. We address the need for written procedures generally in section IV of this document. We also respond to individual comments on specific provisions in the same section.

Final § 111.553 requires that you establish and follow written procedures to fulfill the requirements of this subpart O. Under final § 111.570(b)(1) we require you to make and keep records of such procedures. Such records would be required to be made available to us under the requirements in subpart P.

We encourage you to include in your written procedures the recommendation made in the 2003 CGMP Proposal for you to consult with a health care provider if you receive complaints that involve serious illness or injury. Even if the complaints are not required to be submitted to FDA under the newly enacted “Dietary Supplement and Non-Prescription Drug Consumer Protection Act” (Public Law 109–462), we encourage your company to notify us about the product complaints. Manufacturers and distributors should be aware that this newly enacted law, which requires reporting to FDA of “serious adverse events,” contains new mandatory provisions that require record retention of adverse event reports separate from the requirements in this CGMP final rule concerning product complaints.

E. What Requirements Apply to the Review and Investigation of a Product Complaint? (Final § 111.560)

1. Final § 111.560(a)(1)

Final § 111.560(a)(1) requires a qualified person to review all product complaints to determine whether the product complaint involves a possible

failure of a dietary supplement to meet any of its specifications, or any other requirements of part 111, including those specifications and other requirements that, if not met, may result in a risk of illness or injury. Final § 111.560(a)(1) derives from proposed § 111.95(a).

We did not receive comments specific to proposed § 111.95(a).

2. Final § 111.560(a)(2), (b), and (c)

Final § 111.560(a)(2) requires a qualified person to investigate any product complaint that involves a possible failure of a dietary supplement to meet any of its specifications, or any other requirements of part 111, including those specifications and other requirements that, if not met, may result in a risk of illness or injury. Final § 111.560(b) requires that quality control personnel review and approve decisions by the qualified person about whether or not to investigate a product complaint and the findings and followup action of any investigation performed. Final § 111.560(c) requires that the review and investigation extend to all relevant batches and records.

(Comment 319) Some comments characterize the requirements of proposed § 111.95 as a confusing and difficult scheme to review, investigate, and resolve customer complaints. These comments state the 2003 CGMP Proposal would require extensive human resources, recordkeeping, and decisionmaking.

(Response) We disagree that the 2003 CGMP Proposal would require extensive human resources, recordkeeping, or decisionmaking. The comments provided no rationale for such assertions. The 2003 CGMP Proposal sets forth basic steps, i.e., review, evaluation, and followup, that one would need to take to appropriately address a product complaint. For those product complaints for which there is a reasonable possibility of a relationship to an adverse event, the 2003 CGMP Proposal would require that an investigation be done by the

quality control unit because we believe such an event would need more careful review and followup.

To address the comments that found proposed § 111.90 confusing, we have made the following changes in the final rule to simplify the procedures for handling product complaints:

- We replaced the proposed procedure in which a qualified person determines whether a complaint should be investigated by the quality control unit with a procedure in which a qualified person investigates any product complaint that involves a possible failure of a dietary supplement to meet any requirements of part 111.
- We require an oversight function by quality control personnel for the review and evaluation of product complaints, but do not require that quality control personnel do any investigations. This is consistent with other changes that we are making in response to comments that requested that the quality control unit focus on reviewing tasks performed by others rather than on performing the tasks itself.
- We refer to “any product complaint that involves a possible failure of a dietary supplement to meet any of its specifications, or any other requirements of this part [part 111], including those specifications and other requirements that, if not met, may result in a risk of illness or injury” rather than to “a reasonable possibility of a relationship between the quality of a dietary supplement and an adverse event.” This is consistent with changes that we are making to the definition of the term “product complaint” in final § 111.3 (see section VI of this document).
- We continue to require that the review and investigation of the product complaint extend to all relevant batches and records but simplify the language

of the requirement by removing the details, i.e., that the investigation must include the batch records associated with the dietary supplement involved in the consumer complaint and not specifying that the investigation must extend to other batches of dietary supplement. Rather, we require that the investigation must extend to all relevant batches and records.

The final rule provides firms flexibility on how to use its human resources. Nothing in subpart O would preclude a qualified person among designated quality control personnel to be designated to actually review product complaints and conduct investigations of any product complaint. If an individual is so designated and conducts the investigation, reviews and approves the findings, and conducts followup actions of any investigation performed, final § 111.560(b) would not apply.

(Comment 320) Some comments object to the requirement in proposed § 111.95(c) that consumer complaints are to be investigated only when there may be a relationship between product quality and an adverse event. These comments suggest this provision be extended to any possible relationship between dietary supplements and adverse events, including those that might be independent of whether the product is produced under CGMPs. These comments consider there should be consistent procedures for handling product complaints, regardless of whether the complaints relate to product quality.

(Response) The action requested in these comments is outside the scope of this rule, which specifically addresses CGMP requirements to ensure the quality of the dietary supplement product. However, we encourage firms to investigate all product complaints in a consistent way, regardless of whether the complaints relate to the quality of the dietary supplement.

(Comment 321) Some comments request clarification of statements made or terms used in the preamble to the 2003 CGMP Proposal regarding the handling of product complaints. In the preamble discussion of proposed § 111.95(c), we stated a consumer complaint about adverse effects “after consuming several dietary supplements” is worthy of quality control unit investigation. One comment asks about the meaning of “several” and whether this example means that a manufacturer is responsible for consumers who take more than the recommended dosage.

(Response) In our discussion of proposed § 111.95(c) we addressed a situation where a consumer had symptoms on more than one occasion rather than a situation where a consumer took more than the recommended dosage. However, firms must investigate any complaint of illness or injury even if a consumer reports that he/she has consumed more than the amount recommended on the product label to determine if the complaint is related to CGMP.

F. Under This Subpart, What Records Must You Make and Keep? (Final § 111.570)

1. Final § 111.570(a)

Final § 111.570(a) requires you to make and keep the records required under subpart O in accordance with subpart P. Final § 111.570(a) derives from proposed § 111.95(f)(2) with changes associated with the reorganization.

We did not receive comments specific to proposed § 111.95(f)(2).

2. Final § 111.570(b)(1)

Final § 111.570(b)(1) requires you to make and keep a record of the written procedures for fulfilling the requirements of subpart O. Final § 111.553 requires

written procedures for fulfilling the requirements of subpart O. Those written procedures are considered a record under final § 111.570(b)(1).

3. Final § 111.570(b)(2)

Final § 111.570(b)(2) requires you to make and keep a written record of every product complaint that is related to CGMP. Final § 111.570(b)(2) derives from proposed § 111.95(e) which would require that you “* * * make and keep a written record of every consumer complaint that is related to good manufacturing practices. For the purposes of the regulations in this part, a consumer complaint about product quality may or may not include concerns about a possible hazard to health. However, a consumer complaint does not include an adverse event, illness, or injury related to the safety of a particular dietary ingredient independent of whether the product is produced under good manufacturing practices.”

As a revision for consistency with the definition of “product complaint” in final § 111.3, final § 111.570(b)(2) does not include the two full sentences from proposed § 111.95(e), as quoted in the previous paragraph.

4. Final § 111.570(b)(2)(i)

Final § 111.570(b)(2)(i) requires that the person who performs the requirements of subpart O, at the time of performance, document and record the performance. Final § 111.570(b)(2)(i) is similar to proposed § 111.95(f)(1) with changes associated with the reorganization.

5. Final § 111.570(b)(2)(ii)

Final § 111.570(b)(2)(ii) requires that the written record of the product complaint include: (1) The name and description of the dietary supplement; (2) the batch, lot, or control number of the dietary supplement, if available;

(3) the date the complaint was received and the name, address, or telephone number of the complainant, if available; (4) the nature of the complaint including, if known, how the product was used; (5) the reply to the complainant, if any; and (6) findings of the investigation and followup action taken when an investigation is performed. Final § 111.570(b)(2) is similar to proposed § 111.95(e)(1) through (e)(6) and includes a change we are making after considering comments to proposed § 111.95(e)(4) (discussed in the following paragraphs) which would have required that the consumer complaint written record include “The nature of the complaint including how the consumer used the product.” On our own initiative, we also made a change to include the date the complaint was received.

(Comment 322) One comment notes proposed § 111.95(e)(4) would require the written record of consumer complaints to include “how the consumer used the product.” The comment notes this information may not always be available and suggests the words “where known” should be added.

(Response) We agree that there can be circumstances where the firm that receives the product complaint may not know how the product was used. For example, a consumer may make a complaint by leaving a telephone message before or after business hours and neither describe how the product was used, nor leave contact information so that the firm could followup with the consumer. To address this comment, we provide in the final rule that the written record of the product complaint include “the nature of the complaint including, if known, how the product was used.”

(Comment 323) Some comments request clarification of statements made or terms used in the preamble to the 2003 CGMP Proposal regarding the handling of product complaints. In our discussion of proposed § 111.95(e) we

recommended that consumer complaints and investigations be reported to us when consumption of a dietary supplement may be related to “a serious adverse event.” Some comments note that “serious” is not defined.

(Response) The term “serious adverse event” is widely used in the industries we regulate. Our current forms for reporting “serious adverse events” via the MedWatch program do not define the term, but instead list outcomes that were attributed to an adverse event. These outcomes include death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention to prevent permanent impairment/damage, and “other.” As discussed in this section, however, there is a new statutory requirement for mandatory reporting to FDA of serious adverse events enacted in the “Dietary Supplement and Non-Prescription Drug Consumer Protection Act” (Public Law 109–462). The new law does define “serious adverse events” as those events that result in death, a life-threatening situation, an inpatient hospitalization, a persistent or significant disability or incapacity, or a congenital anomaly or birth defect or one that requires medical or surgical intervention to prevent such serious outcomes (based on reasonable medical judgment). The law also has specific provisions for how these serious adverse events are to be submitted to FDA and record retention for records relating to these and other adverse event reports. We anticipate issuing guidance on implementation of the new statutory provisions. We encourage firms who are unsure as to whether the nature of a reported adverse event should be reported to FDA to contact us for assistance.

XXI. Comments on Records and Recordkeeping (Final Subpart P)

A. Organization of Final Subpart P

In the 2003 CGMP Proposal, the requirements for records and recordkeeping were set forth in proposed § 111.125. As shown in table 17 of this document, we are reorganizing the requirements for records and recordkeeping into a distinct subpart (final Subpart P—Records and Recordkeeping). Table 17 lists the sections in final subpart P and identifies the proposed provisions that form the basis for the final rule.

TABLE 17.—DERIVATION OF SECTIONS IN FINAL SUBPART P

Final Rule	2003 CGMP Proposal
§ 111.605 What requirements apply to the records you make and keep?	§ 111.125(a) and (b)
§ 111.610 What records must be made available to FDA?	§ 111.125(b) and (c)

B. Highlights of Changes to the Proposed Requirements for Records and Recordkeeping

1. Revisions

The final rule reflects that it applies to persons who manufacture, package, label, or hold a dietary supplement unless subject to an exclusion in § 111.1.

2. Changes After Considering Comments

This final rule requires you to keep written records required by this subpart for either 1 year past the shelf life date, if shelf life dating is used, or 2 years beyond the date of distribution of the last batch of dietary supplements associated with those records (final § 111.605(a)).

C. General Comments on Proposed § 111.125

(Comment 324) Some comments support the requirements in proposed § 111.125 because documentation helps to ensure CGMPs are consistently followed and retention of records provides an effective trail when subsequent problems need to be identified and corrected.

Another comment asserts the recordkeeping requirements would represent a large burden for companies that manufacture vitamin and mineral supplements with a large number of active ingredients.

(Response) We agree that records are useful in identifying manufacturing problems and tracking the source of failures in CGMPs.

We understand the burden on manufacturers may be heavier for manufacturers who use many dietary ingredients and discuss the burden of the recordkeeping requirements in sections XXVIII and XXIV of this document. However, we do not believe that a manufacturer who elects to put several components into one finished batch of dietary supplement would necessarily have a larger burden than one who, instead, elects to manufacture multiple dietary supplements each containing one component. We believe that the requirements, for example, for ensuring the identity, purity, strength, and composition of each component in a dietary supplement need to be the same for a dietary supplement containing one ingredient or component and one containing multiple ingredients or components. To the extent the comment is suggesting that the recordkeeping requirements for those who manufacture multivitamin/mineral dietary supplements (containing components) are too large and should be less, the comment provided no basis for such a change.

D. What Requirements Apply to the Records That You Make and Keep? (Final § 111.605)

1. Final § 111.605(a)

Final § 111.605(a) requires you to keep written records for 1 year past the shelf life date, if shelf life dating is used, or 2 years beyond the date of distribution of the last batch of dietary supplements associated with those records. Final § 111.605(a) derives from proposed § 111.125(a).

(Comment 325) Several comments suggest that the requirement in proposed § 111.125(a) to keep records for 3 years beyond the date of manufacture should be modified. One comment favors record retention for 3 years beyond the date of manufacture or for the shelf life of the product, whichever is longer. Some comments state the rule should require establishment of an expiration date and that the manufacturer should have the option of retaining records for 1 year beyond the expiration date, when an expiration date has been established by the manufacturer. Some comments point out that under section 306(a) of the Bioterrorism Act, FDA is authorized to issue recordkeeping regulations with a record retention period of “not longer than two years.” One comment, therefore, asserts CGMP records should not be kept for more than 2 years.

(Response) We believe a record retention period for records related to CGMP requirements should correlate generally with the length of time that product complaints are likely to arise related to the manufacture of a dietary supplement. Such correlation will increase the likelihood that, if a problem with a dietary supplement is identified that may be associated with a violation of CGMP, the dietary supplement manufacturer, packager, labeler, or holder

will have access to the CGMP records associated with that dietary supplement. In addition, we will have access to such records at inspection.

We have modified the final rule to require a record retention period of 2 years beyond the date of distribution of the last batch of dietary supplements associated with those records or 1 year past the shelf life date, if shelf life dating is used.

A significant portion of the dietary supplement industry use shelf life dating. It is likely that if there are product complaints related to a product these will arise during the shelf life of these products. To ensure there is adequate time to examine the records, determine if there are related manufacturing problems, and implement corrective actions, it is necessary to require the retention of records for 1 year past the shelf life date. This will help ensure that establishments have access to such records to perform the necessary CGMP actions.

For those dietary supplements without shelf life or expiration dating, we believe that 2 years from the date of distribution is a reasonable estimate of the time needed to retain records in order to address CGMP problems identified in product complaints.

It is important to note that, as discussed in this section, the term "shelf life dating," includes shelf life dating as well as expiration dating and "best if used by" dating.

We disagree with the comment that suggests we require an expiration date on all products. Many products will not have a determinable expiration date due to the state of knowledge about these products. We believe the manufacturer is in the best position to determine if its product requires an expiration date.

(Comment 326) One comment requests clarification of the “date of manufacture.” The comment asserts if an expiration date is shown on the label of a product, the date of manufacture should be considered to be the date on which the expiration date is based. The comment gives an example of vitamin C tablets having a 2-year shelf life. The comment explains if the tablets are compressed, tested, and approved for packaging in August 2003, they would generally be assigned an expiration date of August 2005 regardless of the date of packaging. The comment argues if the tablets are held and later packaged in February 2004, records for this batch should only have to be kept for 1 year beyond the expiration date (i.e., August 2006), rather than 3 years beyond the packaging date (i.e., February 2007).

(Response) In the scenario described in the previous paragraph, where an expiration date (shelf life) has been determined, records for this batch must only be kept for 1 year beyond the expiration date (i.e., shelf life date). The packaging date in the scenario has no effect on the amount of time records must be kept. However, in the final rule, we have decided that it is more appropriate to determine the record retention period from the date of distribution rather than the “date of manufacture.” The date on which the manufacturer completes the manufacture of a batch of a dietary supplement (the date of manufacture) does not necessarily indicate the availability of the dietary supplement product in the marketplace. It is possible that such product could be held for a period of time before entry into the marketplace and possible consumer consumption. A more accurate time period for entry is calculated by the date of distribution. Final § 111.605(a)(2) requires that manufacturers, packagers, labelers, and holders keep their records for 2 years from the date of distribution of the last batch of dietary supplement associated

with those records. For products with a shelf life date, the records associated with those dietary supplements are required to be kept for 1 year past the shelf life date of that particular dietary supplement. Packagers and labelers that return the product to the manufacturer for distribution are not required to keep separate records under this subpart.

2. Final § 111.605(b)

Final § 111.605(b) requires you to keep records as original records, true copies (such as photocopies, microfilm, etc.), or as electronic records. Final § 111.605(b) derives from proposed § 111.125(b).

We did not receive comments specific to proposed § 111.125(b).

3. Final § 111.605(c)

Final § 111.605(c) requires that all electronic records comply with part 11 (21 CFR part 11). Final § 111.605(c) derives from proposed § 111.125(b).

(Comment 327) One comment believes part 11 should only apply to records that do not have paper counterparts.

(Response) This comment is beyond the scope of this CGMP rulemaking.

(Comment 328) One comment suggests the proposed requirement that CGMP electronic records must comply with part 11 should be deleted because the FDA guidelines on part 11 have not yet been finalized.

(Response) Part 11 applies to electronic CGMP records. Therefore, final § 111.605(c) requires that all electronic records, including electronic signatures, must comply with part 11. We have finalized guidance for industry. The guidance entitled “Part 11, Electronic Records; Electronic Signatures Scope and Application,” sets out our enforcement policies with respect to certain aspects of part 11 (Ref. 33). The guidance is available at <http://www.fda.gov/>

der/guidance/5667fnl.htm. The guidance applies to any CGMP electronic records and signatures.

E. What Records Must Be Made Available to FDA? (Final § 111.610)

1. Final § 111.610(a)

Final § 111.610(a) requires you to keep records, or copies of such records, required by this final rule, readily available during the retention period for inspection and copying by FDA when requested. Final § 111.610(a) derives from proposed § 111.125(c). We responded in section V of this document to comments that we received on FDA's statutory authority to inspect and copy records. We made one editorial, nonsubstantive change from the language in proposed § 111.125(c). We removed the word "authorized" to prevent any confusion regarding whether some authorization other than the statutory authority that provides the legal basis for this final rule is necessary for our access to inspect and copy records.

2. Final § 111.610(b)

Final § 111.610(b) requires that if you use reduction techniques, such as microfilming, you must make suitable reader and photocopying equipment readily available to us. Final § 111.610(b) derives from proposed § 111.125(b).

We did not receive any comments specific to proposed § 111.125(b) and final § 111.610(b).

XXII. Other Comments and Miscellaneous

A. Comments on Guidance Documents To Be Used With the Final Rule

In the 2003 CGMP Proposal, we invited comment on the usefulness of guidance documents, education, training, or other approaches and potential sources of education and training that would assist industry efforts to

implement the 2003 CGMP Proposal, if finalized as proposed (68 FR 12157 at 12163).

(Comment 329) A few comments state booklets, videos, seminars, and other training would be useful on topics such as sanitation, recordkeeping, quality assurance methods, microbiological testing, and botany. Another comment states a subset of CGMPs that focuses on plant authenticity, purity, proper handling, and hygiene should be developed for parties who exclusively deal with bulk raw agricultural commodities (with the exception of individual wildcrafters). If such CGMPs are not developed, the comment requests we develop guidance documents on the identification, cultivation, and handling of botanicals. The same comment also notes guidance specifically is needed on the use of microscopy to identify plants.

(Response) We acknowledge these comments and, in the future, we may issue guidance that relates to certain dietary supplement CGMP requirements.

B. Comments on Consideration for Other CGMP Programs

(Comment 330) One comment asserts several existing dietary supplement CGMP programs (e.g., those developed by the NNFA, NSF International, ANSI, and USP) are well designed and represent useful examples for us to follow. The comment notes section 12(d) of the National Technology Transfer and Advancement Act directs Federal agencies to use such voluntary consensus standards whenever possible, as long as the standards are consistent with Federal law and are practical. The comment recommends we include standards from these existing CGMP programs where suitable in the final rule.

(Response) In the development of the 2003 CGMP Proposal and this final rule, we carefully considered the comments that recommended aspects of other CGMP programs. For example, as discussed previously, the 1997 ANPRM for

this rule contained the entire text of an outline presented to us by representatives of the dietary supplement industry. Furthermore, where comments recommended aspects of other CGMP programs, we considered those recommendations and, in some cases, incorporated certain recommendations into requirements in this final rule (e.g., the use of a certificate of analysis).

In 2006, ANSI updated its Standard 173 (ANSI Standard 173) regarding dietary supplements (Ref. 35). ANSI Standard 173 contains provisions for dietary supplement CGMP that are based, in part, on the industry submission to FDA in November 1995, which the agency published as part of its 1997 ANPRM. We considered comments to the 1997 ANPRM, many of which commented on the provisions of the industry submission, and the comments to the 2003 CGMP Proposal in the course of developing this CGMP final rule. We have considered the provisions contained in the updated ANSI Standard 173 and many of the specific provisions contained in ANSI Standard 173 are similar to provisions adopted in this final rule. For example, both the ANSI standard and this CGMP final rule have similar requirements on written procedures, personnel qualifications, record retention, and quality control. However, we determined that adopting the entire ANSI Standard 173 would be impracticable. There are key provisions which reflect major differences between the latest ANSI Standard 173 and the CGMP final rule. Many of these differences are in the product testing environment. For example, the ANSI standard contains different product testing frequency and production stage requirements. We have extensively discussed the justification for the particular testing requirements adopted in this CGMP final rule, which we believe are no more burdensome than the ANSI Standard 173 requirements. For example,

the ANSI Standard 173 contains testing methods for metal or microbiological contaminants not included in the final rule. We found that providing flexibility for manufacturers to choose their own specific test methods was a more efficient way of reaching the goals of the CGMP final rule than specifying and requiring particular tests. We support, however, the use of the ANSI Standard 173 testing methods by manufacturers, where appropriate, in complying with the requirements of this rule.

(Comment 331) Another comment states CGMPs that reflect common elements and areas of uniqueness should be placed in subcategories of CGMPs as is the case with the current food CGMP model. The comment recommends we follow a similar approach and establish subcategories of CGMPs for dietary supplements (e.g., for vitamin-mineral and probiotic tablets).

(Response) In the 1997 ANPRM, we asked for comment about whether broad CGMP regulations would be adequate, or whether it would be necessary to address the operations of particular segments of the dietary supplement industry (68 FR 12157 at 12174). Based on the comments received to the 1997 ANPRM, we were persuaded that a broad final rule is preferable to multiple regulations focused on particular segments of the dietary supplement industry, or to general CGMP provisions plus subcategories applicable to segments of the dietary supplement industry. We stated in the 2003 CGMP Proposal that we would consider whether we needed to re-evaluate our decision to establish one set of requirements for all dietary supplements (*id.*). This comment did not provide any basis to persuade us to re-evaluate the decision we made that a broad CGMP rule was appropriate. Thus, in this final rule, we are establishing one set of requirements for all persons who manufacture, package,

label, or hold dietary supplements and not subject to an exclusion under final § 111.1.

C. Comments on Public Involvement

1. Public Involvement

(Comment 332) Several comments express general concerns with our public involvement process. Several comments state additional public meetings and workshops are necessary to permit FDA, industry, and other stakeholders to work together to seek a more workable solution to dietary supplement CGMPs and to resolve differences of opinion. One comment states the differences of opinion identified by the comment process will not be meaningfully resolved without active and forthright communication with stakeholders. According to the comment, we should establish a forum prior to the publication of the final rule to communicate our perception of these differences of opinion. In another comment, a trade association expresses disappointment that our 2003 CGMP Proposal disregards industry efforts to draft CGMPs over the last decade. Another comment contends the proposal was rushed and the comment period was established without publication of a core economic analysis to support it.

(Response) We disagree with these comments. We believe there has been sufficient public involvement given the public meetings that were held and the opportunity for comment during the comment periods provided. We discuss the public involvement in section I of this document. Further, the 2003 CGMP Proposal did contain an economic analysis. We received extensive comments on the economic analysis in the 2003 CGMP Proposal. We have made several changes to the economic analysis of this final rule in response to these comments as discussed in section XXIV of this document.

Furthermore, we have made various changes in response to comments to the CGMP requirements in this final rule.

D. Comments on Implementation and Enforcement

(Comment 333) Several comments suggest postponing the effective date of the rule for 24 months to allow a voluntary inspection and compliance program to take effect in the interim. One comment recommends adoption of a voluntary program similar to that of OSHA regulations in Title 29 of the Code of Federal Regulations, where companies would invite FDA inspection without penalty or cost unless a serious violation occurs. In cases of serious violation, companies would have the option to voluntarily correct the problem and inform the public before the effective date of the rule.

(Response) We disagree with these comments regarding the establishment of a voluntary compliance period. The effective date of this final rule is 60 days after the date of its publication in the **Federal Register**. However, as discussed in sections VI and XXIV of this document, we have staggered compliance dates to 12 months, 24 months, and 36 months, respectively, after the final rule's publication date for businesses of over 500 employees, businesses with under 500 employees but 20 or more employees, and businesses with less than 20 employees.

(Comment 334) Several comments indicate they want differential treatment under the final rule based on the seriousness of a violation, others ask for strict enforcement, and others ask how FDA would enforce against those who continually adulterate dietary supplements.

(Response) We consider these comments to be outside the scope of this final rule. In general, we would provide guidance on our enforcement policy

through the issuance of guidance documents if we determine that any variance from full enforcement is warranted.

(Comment 335) Another comment expresses concern the 2003 CGMP Proposal works at “cross purposes” with recent regulations associated with bioterrorism. The comment recommends these rules be harmonized to reduce costs and increase efficiencies for manufacturers.

(Response) It is not clear what the comment means when it states the 2003 CGMP Proposal works at “cross purposes” with the regulations issued under the Bioterrorism Act or that we should “harmonize” the regulations issued under the Bioterrorism Act with the final rule establishing dietary supplement CGMP requirements. We have made every effort to consider the regulations issued under the Bioterrorism Act and their relationship to this final rule. There are different purposes to the Bioterrorism Act and these CGMP requirements; however, we have harmonized to the extent possible.

(Comment 336) One comment states the 1-year compliance period for large firms is reasonable as long as we modify the rule to better reflect existing CGMPs already in practice among responsible companies. The comment also notes the 3-year compliance period for small firms may be reasonable, but urges us to enforce compliance of basic food GMP requirements, which some of these firms may not be observing.

(Response) The effective date for this final rule is 60 days after its date of publication in the **Federal Register**, though we are staggering the compliance dates as described in sections VI and XXIV of this document. Dietary supplement products in the marketplace must already be in compliance with all other statutory and regulatory provisions that affect dietary supplements.

E. Removal of References to Part 112

The 2003 CGMP Proposal (68 FR 12157 at 12175) had proposed the heading and table of contents for part 112. Proposed part 112 had the heading “Restrictions for Substances Used in Dietary Supplements.” At the time, we said that it was necessary to amend part 112 because at that time the proposed rule for dietary supplements containing ephedrine alkaloids (62 FR 30678, June 4, 1997) had not been finalized and included proposed revisions to part 111. The 2003 CGMP Proposal for dietary supplement CGMPs proposed using part 111 and proposed the relocation of the “Restrictions for Substances Used in Dietary Supplements” to part 112. Since the issuance of the 2003 CGMP Proposal, the final rule for dietary supplements containing ephedrine alkaloids has been finalized (69 FR 6788, February 11, 2004) and has been included in 21 CFR part 119. Thus, there is no need to reserve part 112 in this final rule. The references to part 112 have been removed from the final rule.

XXIII. Paperwork Reduction Act of 1995

This final rule contains information collection requirements that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501–3520). The title, description, and respondent description of the information collection requirements are given in the following paragraphs, with estimates of the one-time burden of establishing written procedures and the annual recordkeeping burden. Included in the burden estimates are the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing each collection of information.

Title: Current Good Manufacturing Practice in Manufacturing, Packaging, Labeling, or Holding Operations for Dietary Supplements

Description: Section 402(g) of the act gives us explicit authority to issue a rule establishing current good manufacturing practice requirements for dietary supplements. Section 402(g)(1) of the act states that a dietary supplement is adulterated if “it has been prepared, packed, or held under conditions that do not meet current good manufacturing practice regulations.” Section 402(g)(2) of the act authorizes us to, by regulation, “prescribe good manufacturing practices for dietary supplements.” Under section 701(a) of the act (21 U.S.C. 371), FDA may issue regulations necessary for the efficient enforcement of the act. Other relevant legal authority is discussed in section V of this document.

We did not receive any direct comments on the Paperwork Reduction Act analysis of the 2003 CGMP Proposal. Many comments on the estimated costs of the 2003 CGMP Proposal stated that we underestimated the annual number of batches of dietary supplements produced. Due to a contractor’s error, we did underestimate the number of batches produced. This final paperwork reduction analysis corrects for this error. The final analysis also has been revised from the analysis of the 2003 CGMP Proposal in order to incorporate the effects of revisions to the proposed regulation, including reorganization.

Records are an indispensable component of CGMP. The records required by this final rule provide the foundation for the planning, control, and improvement processes that constitute a quality control system.

Implementation of these processes in a manufacturing operation serves as the backbone to CGMP. The records will show what is to be manufactured; what was, in fact, manufactured; and whether the controls that the manufacturer put in place to control the identity, purity, strength, and composition and limits on contaminants and to prevent adulteration were effective. Further,

records will show whether and what deviations from control processes occurred, facilitate evaluation and corrective action concerning these deviations (including, where necessary, whether associated batches of product should be recalled from the marketplace), and enable a manufacturer to assure that the corrective action was effective. Further, records will show whether and what deviations from control processes occurred, facilitate evaluation and corrective action concerning these deviations (including, where necessary, whether associated batches of product should be recalled from the marketplace), and enable a manufacturer to assure that the corrective action was effective. In addition, by requiring records, we will be able to ensure that you follow CGMPs so that you ensure the quality of your dietary supplements during manufacturing, packaging, labeling, or holding operations. The final rule establishes the minimum manufacturing practices necessary to ensure that dietary supplements are manufactured, packaged, labeled, or held in a manner that will ensure the quality of the dietary supplements during manufacturing, packaging, labeling or holding operations.

The records requirements of this final rule include written procedures and records pertaining to: (1) Personnel; (2) sanitation; (3) calibration of instruments and controls; (4) calibration, inspection, or checks of automated, mechanical, or electronic equipment; (5) maintaining, cleaning, and sanitizing equipment and utensils and other contact surfaces; (6) water used that may become a component of the dietary supplement; (7) production and process controls; (8) quality control; (9) components, packaging, labels and product received for packaging and labeling; (10) master manufacturing and batch production; (11) laboratory operations; (12) manufacturing operations; (13)

packaging and labeling operations; (14) holding and distributing operations; (15) returned dietary supplements; and (16) product complaints.

Description of Respondents: Manufacturers, dietary supplement manufacturers, packagers and re-packagers, labelers and re-labelers, holders, distributors, warehouseers, exporters, importers, large businesses, and small businesses.

The recordkeeping requirements of the final rule are set forth in each subpart. In table 18 of this document we list the one-time burdens associated with establishing written procedures. In table 19 of this document we list the annual burdens associated with recordkeeping. In each table, where the same records are mentioned in more than one provision of a subpart, we list the burden under the provisions corresponding to the heading, "Under this subpart, what records must you make and keep?" For some provisions listed in table 19, we did not estimate the annual frequency of recordkeeping because recordkeeping occasions consist of frequent brief entries of dates, temperatures, monitoring results, or documentation that specific actions were taken. Information might be recorded a few times a day, week, or month. When the records burden involves frequent brief entries, we entered one as the default for the annual frequency of recordkeeping. For example, many of the records listed under final § 111.35 in table 19, such as final § 111.35(b)(2) (documentation, in individual equipment logs, of the date of the use, maintenance, cleaning, and sanitizing of equipment), involve many short sporadic entries over the course of the year, varying across equipment and plants in the industry. We did not attempt to estimate the actual number of recordkeeping occasions for these provisions, but instead entered an estimate of the average number of hours per year. We entered the default value of 1

as the annual frequency of recordkeeping for these and similar provisions. For final § 111.35, the entry for annual frequency is 1 as a default representing a large number of brief recordkeeping occasions.

In many rows of tables 18 and 19 of this document, we list a burden under a single provision that covers the written procedures or records described in several provisions. The burden of the master manufacturing record listed in table 18 under final § 111.210 includes the burden for final § 111.205 because the master manufacturing record must include those written procedures. Similarly, the burden of the batch production records listed in table 19 under final § 111.260 includes the burden for records listed under final § 111.255 because the batch production records must include those records.

The annual frequency for batch production records (and other records kept on a batch basis in table 19 of this document) equals the annual number of batches. The estimated burden for records kept by batch includes both records kept for every batch and records kept for some but not all batches. We use the annual number of batches as the frequency for records that will not necessarily be kept for every batch, such as test results or material review and disposition records, because such records are part of records, if they are necessary, that will be kept for every batch.

We estimate the burden of this collection of information as follows:

TABLE 18.—ESTIMATED ONE-TIME BURDEN TO ESTABLISH WRITTEN PROCEDURES¹

21 CFR Section	Number of Recordkeepers	Annual Frequency per Recordkeeping	Total Records	Hours per Record	Total Hours
111.14	15,000	1	15,000	3.6	54,000
111.23	15,000	1	15,000	1	15,000
111.35	400	1	400	36	14,400
111.95	250	1	250	68	17,000
111.140	300	1	300	10.7	3,210
111.180	200	1	200	10	2,000
111.210	250	1	250	12	3,000

TABLE 18.—ESTIMATED ONE-TIME BURDEN TO ESTABLISH WRITTEN PROCEDURES¹—Continued

21 CFR Section	Number of Recordkeepers	Annual Frequency per Recordkeeping	Total Records	Hours per Record	Total Hours
111.325	150	1	150	45	6,750
111.375	260	1	260	9	2,340
111.430	250	1	250	12.6	3,150
111.475	15,000	1	15,000	2.1	31,500
111.535	200	1	200	6	1,200
111.570	240	1	240	12	2,880
Total					156,430

¹There are no capital costs or operating costs associated with the collection of information under this final rule.

TABLE 19.—ESTIMATED ANNUAL RECORDKEEPING BURDEN¹

21 CFR Section	Number of Recordkeepers	Annual Frequency per Recordkeeping	Total Annual Records	Hours per Record	Total Hours
111.14	15,000	4	60,000	1	60,000
111.23	15,000	1	15,000	0.2	3,000
111.35	400	1	400	12.5	5,000
111.95	250	1	250	45	11,250
111.140	240	1,163	279,120	1	279,120
111.180	240	1,163	279,120	1	279,120
111.210	240	1	240	2.5	600
111.260	145	1,408	204,160	1	204,160
111.325	120	1	120	15	1,800
111.375	260	1	260	2	520
111.430	50	1	50	12.6	630
111.475	15,000	1	15,000	0.4	6,000
111.535	110	4	440	13.5	5,940
111.570	240	600	144,000	0.5	72,000
Total					929,140

¹There are no capital costs or operating costs associated with the collection of information under this final rule.

The burden estimates in tables 18 and 19 of this document are based on our institutional experience with other CGMP requirements and on data provided by Research Triangle Institute (RTI) in the “Survey of Manufacturing Practices in the Dietary Supplement Industry,” OMB Control Number 0910–0422, expiration date April 4, 2000 (Refs. E1 and E2).

The estimates in both tables of the number of firms affected by each provision of the rule are based on the percentage of manufacturers, packagers, labelers, holders, distributors, and warehouseers that reported in the survey that

they have not established written SOPs or do not maintain records that would be required under the final rule. Because we do not have survey results for general warehouses, we entered the approximate number of facilities in that category for those provisions covering general facilities. For the dietary supplement industry, the survey estimated that 1,460 firms would be covered by this final rule, including manufacturers, packagers, labelers, holders, distributors, and warehouseers. The time estimates include the burden involved in documenting that certain requirements are performed and in recordkeeping. We used an estimated annual batch production of 1,408 batches per year to estimate the burden of requirements that are related to the number of batches produced annually, such as final § 111.260, "What must the batch production record include?" The estimate of 1,408 batches per year is near the midpoint of the number of annual batches reported by survey firms.

The length of time that CGMP records must be maintained is set forth in final § 111.605. Tables 18 and 19 of this document reflect the estimated burdens for written procedures, record maintenance, periodically reviewing records to determine if they may be discarded, and for any associated documentation for that activity for records that will be required under part 111. We have not included a separate estimate of burden for those sections that require maintaining records in accordance with final § 111.605, but have included those burdens under specific provisions for keeping records. For example, final § 111.255(a) requires that the batch production records be prepared every time a batch is manufactured, and final § 111.255(d) requires that batch production records be kept in accordance with final § 111.605. The estimated burdens for both § 111.255(a) and (d) are included under final § 111.260 (what the batch record must include).

The information collection provisions of this final rule have been submitted to OMB for review.

Prior to the effective date of this final rule, we will publish a document in the **Federal Register** announcing OMB's decision to approve, modify, or disapprove the information collection provisions in this final rule. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

XXIV. Analysis of Impacts

A. Introduction

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

The Small Business Regulatory Enforcement Fairness Act of 1996 (Public Law 104-121) defines a major rule for the purpose of congressional review

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

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

The Unfunded Mandates Reform Act of 1995 (Public Law 104–4) requires cost-benefit and other analyses for rules that would cost more than \$100 million in a single year. The current (2005) inflation-adjusted statutory threshold is \$122 million. This final rule qualifies as a significant rule under the statute.

1. Summary of the Economic Analysis

We carry out the cost-benefit analyses required for significant rules in the Final Regulatory Impact Analysis, in section XXIV.B of this document. We perform the Final Regulatory Flexibility Analysis of the effects on the final rule on small businesses in section XXIV.C of this document. We estimate that, once it is fully implemented 36 months after the date of publication, the quantifiable annual benefits from the final rule will be about \$44 million. The

benefits able to be quantified are generated by more consistently produced dietary supplements which will increase product safety, which reduces the number of acute illnesses and product recalls. In addition, the final rule may generate benefits that we lack sufficient data to quantify. These benefits we cannot quantify arise from dietary supplements manufactured under a system to ensure quality, which leads to a reduction in the number of chronic illnesses and conditions.

The final rule will lead to quantifiable costs of \$16 million in the first year it takes effect, \$120 million in the second year, and \$190 million in the third year. After 3 years, the annual costs will be about \$164 million. If we annualize the benefits and costs over 20 years at a 3 percent rate of discount, the annualized quantifiable benefits are \$40 million and annualized quantifiable costs are \$153 million. These annualized benefits include only those that we are able to quantify. The total annualized benefits may be larger than our estimate of \$40 million in quantifiable benefits because of the benefits that we are not able to quantify.

We have determined, based on information contained in this regulatory impact analysis as well as information contained elsewhere in the preamble, that the benefits of this final rule justify the costs.

The final rule will have a significant economic effect on small businesses. We estimate that the annual costs will be about \$46,000 for an establishment with fewer than 20 employees and \$184,000 for an establishment with 20 to 499 employees.

2. Summary of Comments on the Economic Analysis

We received numerous substantive comments on the economic analysis of the 2003 CGMP Proposal. In general, comments from the dietary supplement

industry state that we underestimated the cost of the 2003 CGMP Proposal. Specific comments from the industry target the 2003 CGMP Proposal's testing requirements, which the comments characterize as "burdensome." Many comments address our estimate of the number of batches of dietary supplements firms produce in a year. Many comments express the fear that, as a result of this 2003 CGMP Proposal, the prices consumers pay for dietary supplements would increase dramatically. Nearly all economic comments mention potential adverse effects of the 2003 CGMP Proposal on small businesses, stating that many firms would have to stop manufacturing. A few comments state that, if made final, the 2003 CGMP Proposal would make dietary supplements more expensive than pharmaceuticals. Other comments address the following topics:

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

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

B. Final Regulatory Impact Analysis

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

The final rule is needed because establishments that manufacture, package, label, or hold dietary supplements may not have sufficient market incentives to use controls to ensure that the characteristics of the supplements are what consumers would choose to buy if they had full or adequate information.

Dietary supplements have the characteristics of both experience goods and credence goods.¹² In terms of the acute illnesses discussed below, it may be difficult for consumers to identify the attributes of dietary supplements before the actual consumption of the good. Therefore, it may be difficult, in the absence of some regulation of dietary supplement manufacturing practices, for consumers to differentiate between products produced under good manufacturing practices, and those that are not, at the point of purchase in the marketplace. In terms of dietary supplements as credence goods, consumers may never have adequate information on product characteristics even after the consumption of the good, making it difficult for consumers to determine what benefits each product offers. Because problems can be undetectable, establishments may not adopt the necessary practices to ensure product attributes are as they are intended unless required to do so by regulation.

Of course, the characteristics of dietary supplements, as a type of food product, argue for some sort of Government intervention in this market in order to alleviate the specific market failures that lead to the types of problems with dietary supplements that this rule addresses. There are many types of interventions that may be used to address market failure; FDA has examined the options and has determined that specific CGMPs are necessary for dietary supplements. The rest of this regulatory impact analysis, and particularly section III.A of this document, discusses why FDA has concluded that specific CGMPs are necessary for dietary supplements.

(Comment 337) We received several comments on the need for the 2003 CGMP Proposal. Four comments specifically support the proposal, stating, in

¹²An experience good is a product or service where product characteristics such as quality or price are difficult to observe in advance, but these characteristics can be ascertained upon consumption. A credence good is a good whose utility impact is difficult or impossible for the consumer to ascertain even after consumption of the good.

part, that they are pleased we are addressing the issue of dietary supplement manufacturing. In addition, one comment states that the 2003 CGMP Proposal was a good step toward providing assurance that dietary supplements are as safe as prescription and OTC drugs.

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

One comment states that the 2003 CGMP Proposal spells out design standards rather than performance standards. According to the comment, the 2003 CGMP Proposal spells out procedures a firm must follow rather than defining a specific outcome, such as a specified level of contamination. This comment maintains that we should set a performance standard and then allow manufacturers flexibility in how that standard is reached. Another comment states that, although certain dietary supplement ingredients may cause concern, this concern did not justify imposing “overbearing” and “broad”

CGMP regulations for an entire industry. Another comment asserts that the CGMPs as presented in the 2003 CGMP Proposal would serve as an anti-competitive tool by allowing dominant manufacturers to increase their dominance and make it more difficult for new firms to enter the industry.

(Response) Those comments that disagreed with our analysis provided no data or evidence to support the comment. Without such data or evidence, we have no basis upon which to revise our analysis and continue to use the analysis. Thus, we have not made any changes based on these comments.

Whether or not these provisions are performance or design standards is a theoretical issue. Instead of specifically choosing either design or performance standards for all provisions of the rule, FDA has chosen to provide flexibility to manufacturers whenever possible. For example, providing for the use of "safe and sanitary" water sources gives manufacturers flexibility in deciding the best way to assure that "safe and sanitary" water is used in the manufacture of their products. There are many areas of the rule where more than one way is given to comply with a particular provision. This flexibility allows manufacturers to choose the appropriate means to comply with the provision that is the most cost-effective for them.

We agree with the comments that point out that existing statutes and regulations, concern for brand names, and voluntary industry standards provide some product safety and quality. Nonetheless, continuing problems in the industry provide evidence for the need for this final rule. From 2000 through 2005, there were a total of 75 recall actions in the dietary supplement industry, including class 1, 2, and 3 recalls of vitamins and minerals and herbal and botanical supplements. We will discuss these recalls, which accounted for about 4 percent of the 1,937 FDA food recall actions in 2000

through 2005, later in this document. Most of these recalls occurred because establishments failed to adhere to product manufacturing or labeling specifications.

For a class 1 recall, there is a reasonable probability of serious adverse health consequences or death; for a class 2 recall, exposure to the product may cause temporary or medically reversible adverse health consequences; for a class 3 recall, exposure to the product is not likely to cause adverse health consequences. Full compliance with the provisions of this final rule could have prevented most of the recalls. We note also recall classifications only track acute hazards, not long-term quality problems. Results from ConsumerLab.com and other independent laboratory results provide further evidence of a need for this final rule (Refs. E3 through E6). Statistical sampling methods were not used to collect the data reported in these analyses. Therefore, although this information provides anecdotal evidence of problems, the data may not be representative of overall industry practices. The information serves as additional evidence of the existence of problems.

Although the final rule will increase the monetary cost of entering the dietary supplement industry, the industry will remain highly competitive with more than a thousand competing producers and thousands more potential entrants.

2. Regulatory Options

We considered several regulatory options for dealing with current manufacturing, packaging, labeling, and holding practices that may not ensure the quality of the dietary supplement. The options considered include: (1) No new regulatory action, (2) fewer requirements for vitamins and minerals, (3) more restrictive regulations than the final rule, (4) HACCP without the other

elements of the final rule, (5) final product testing only, (6) a final rule for high-risk products or hazards only, and (7) the 2003 CGMP Proposal.¹³ As a result of comments on the 2003 CGMP Proposal and our reconsideration of our position on several provisions, this final rule differs from the 2003 CGMP Proposal.

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

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

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

¹³Options 1 through 6 were discussed in detail in the 2003 CGMP Proposal (68 FR 12157 at 12221 through 12223; March 13, 2003) and analyses of costs were provided when possible. The principles of the options discussion have not changed and are still relevant for purposes of the requirements of the final rule. The 2003 CGMP proposal also included an Analysis of Impacts which contained some errors from a contractor's report. We have corrected the analysis and have recalculated the costs of the 2003 CGMP Proposal. These corrections and recalculations are discussed in section XXIV.B.9 of this document.

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

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

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

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

One comment supporting HACCP stated that the detailed manufacturing and testing requirements of the 2003 CGMP Proposal would, compared with HACCP, stifle innovation. Although regulations that impose costs can divert resources away from innovation, the costs of this final rule represent less than 1 percent of industry revenues (see table 35 of this document). Because research and development expenditures account for a small fraction of total expenditures, any reduced expenditures on research and development

associated with this final rule will be a small fraction of 1 percent of revenues. Thus, it seems unlikely that this rule would have the effect of stifling innovation. As we explained in the economic analysis of the 2003 CGMP Proposal, the HACCP option would not specify detailed manufacturing requirements but would also fail to ensure product quality (68 FR 12157 at 12222). In section X.I of this document, we discuss why HACCP is not appropriate for dietary supplements. The comment supporting HACCP failed to provide any data or any evidence to support its conclusion. Without such data or evidence, we have no basis upon which to revise our analysis and continue to use the analysis.

3. Coverage of the Final Rule

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

TABLE 20.—COVERED ESTABLISHMENTS BY TYPE OF OPERATION FROM THE DIETARY SUPPLEMENT ENHANCED ESTABLISHMENT DATABASE (DS-EED)

Establishment Type	No. of Establishments	Percent of Establishments
Manufacturer	1,228	84.1
Repackager; relabeler	26	1.8
Holder	114	7.8
Establishments not already classified	92	6.3
Total	1,460	100.0

TABLE 21.—COVERED ESTABLISHMENTS THAT HOLD DIETARY SUPPLEMENTS

Type of Holders	NAICS Code	No. of Establishments
General grocery wholesalers or drug wholesalers	424410	4,036
General warehouse	493110	4,415
Drug wholesalers	42420	7,418
Total		15,869

We consulted several sources to estimate the number of establishments reported in this document. The number, 1,460, is the estimated number of establishments in the DS-EED that manufacture, package, label, or hold dietary supplement products in the United States. In the analysis of the 2003 CGMP Proposal, we included an additional 106 U.S. establishments that supplied dietary ingredients. Because those establishments are not covered in this final rule, we exclude them from the total. RTI developed the DS-EED using FDA's Official Establishment Inventory and supplemented that source with information from trade organizations, trade shows, and electronic databases (Refs. E1 and E2).

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

establishments that would not hold dietary supplements and therefore exclude them from the total.

Foreign firms that export dietary supplements to the United States must satisfy the requirements of this final rule. We do not have data on the number of foreign firms that export dietary supplements to the United States. The small number of foreign products in the FDA dietary supplement sales database suggests that relatively few foreign firms export dietary supplements to the United States (Ref. E7). The foreign firms that will be most affected by the final rule are suppliers of dietary ingredients. Although suppliers of dietary ingredients are not directly covered by the final rule, the need of manufacturers to meet the ingredient specifications required by the final rule will indirectly affect foreign suppliers (as well as domestic suppliers).

No comments were received on the economic analysis of the coverage of the 2003 CGMP Proposal.

4. Baseline Practices

a. *Consumption.* Baseline risks depend on baseline consumption of dietary supplements. Total sales in 2004 were about \$20 billion (Ref. E8). Vitamins and minerals accounted for about 42 percent of sales. Sales of herbal supplements, which have not grown in recent years, were half as large as sales of vitamin and minerals, accounting for about 21 percent of the total. Amino acids, proteins, animal extracts, tea-like supplements, and other supplements not otherwise classified accounted for the remainder of sales.

There were no comments on the consumption baseline.

b. *Manufacturing.* We contracted with RTI to conduct a survey of the dietary supplement industry to learn about both baseline (existing) manufacturing practices and the existing standards used for manufacturing

dietary ingredients and dietary supplements (Ref. E2). A sample of 966 dietary supplement establishments from the DS-EED database was selected from an estimated eligible population of 1,566 firms in the industry (the total number of dietary supplement establishments included 106 ingredient manufacturers, who are now excluded from the requirements of the final rule). The eligibility criteria and the response rate for the survey are fully explained in the final report on the survey (Ref. E2). We further classified the target firms by product and by size. The product categories were: (1) Vitamins and minerals; (2) amino acids and proteins; (3) herbals and botanicals, including extracts; and (4) supplements not already classified.

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

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

TABLE 22.—NUMBER OF COMPLETED SURVEYS BY SAMPLING STRATA

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

(Comment 339) We received two comments on manufacturers’ baseline practices. One comment expresses concern that, as the information is over 3 years old, it may no longer represent current industry practices. The second comment questions the way we calculated the number of dietary supplement

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

(Response) Although the survey responses are now over 6 years old, they represent the best information we have on the industry and its practices. We have, however, adjusted our estimated costs to reflect the correction of the results from the original survey.

5. Baseline Risk

The current number of illnesses caused by poor dietary supplement manufacturing practices requires data linking illnesses to poor practices. Because these data do not exist, we looked for other information to provide indirect evidence on the problem. We looked at many sources for information, including medical and other literature on adverse events, information from poison control centers, reports to the agency, newspaper and magazine articles, and surveys of users. The literature review was conducted using Medline, Healthstar, Aidsline, Cancerlit, and OldMedline (Ref. E9). We found evidence of many adverse events associated with dietary supplements. For example, in 2003, the American Association of Poison Control Centers received 24,412 reports on events associated with herbal dietary supplements and 57,801 reports on events associated with vitamin and mineral supplements, with 8,653 of the herbal and 5,669 of the vitamin and mineral reports treated in health

care facilities (Ref. E10). In addition, we have received many voluntary reports of illnesses caused by dietary supplements (Ref. E11).¹⁴

The vast majority of these events and those described in other sources we consulted, however, are reported as associated with the ingredients used in the products themselves, not with contamination or other results of poor manufacturing processes. Most of the reports from poison control centers on vitamins and minerals, for example, involved inappropriate ingestion by children (Ref. E10). We have no direct evidence on how many illnesses can be attributed to manufacturing processes. The anecdotal evidence described elsewhere in the preamble suggests that many illnesses could have been caused by poor manufacturing processes, but there are only a few examples of evidence that explicitly link illnesses to manufacturing processes. Examples of illness that were linked directly to poor manufacturing practices include vitamin D toxicity from excessive vitamin D in multivitamins and cardiac glycoside poisoning from botanical dietary supplements contaminated with *Digitalis lanata* (Ref. E12).

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

¹⁴Mandatory reporting to FDA of serious adverse events is now required as a result of the enactment of the "Dietary Supplement and Non-Prescription Drug Consumer Protection Act" (Public Law 109-462), signed into law on December 22, 2006. The new law requires manufacturers, packers, or distributors of such products to submit reports to FDA about serious adverse events involving such products based on specific information that they receive from the public.

that manufacturing mistakes exist, so we can construct a plausible link between manufacturing mistakes and potential illnesses or injuries. The number of illnesses associated with a manufacturing problem leading to a recall is both variable and uncertain, and could be anything from zero to quite large. Based on data from FDA food and dietary supplement recalls, we concluded that one reported illness per recall is a plausible average, so we assumed that a recall could be a proxy for a single reported illness associated with a defective product.

Because there are no active surveillance systems for identifying adverse health events related to dietary supplements, we assume that the total number of illnesses caused by poor manufacturing practices is substantially greater than the number reported.¹⁵ Based on data for drug and vaccine reporting rates in other studies, one study concluded that for dietary supplements, reported illnesses represent approximately 1 percent of total illnesses (Ref. E13). We use the associated multiplier, 100, in our baseline estimate and assume that reporting adverse health events due to poorly manufactured dietary supplements occurs at the same rate as reporting adverse health events caused for other reasons by dietary supplements. Other reporting rates and associated multipliers are, however, plausible. For some hazards that lead to severe events only, we have used a multiplier of 10; the Centers for Disease Control and Prevention have used a multiplier of 38 for *Salmonella* infections and similar food-related illnesses. We show the sensitivity of benefits to the choice of multiplier below.

From 1990 through 1999, we received reports on an annual average of 11.8 class 1 and class 2 recalls of dietary supplements related to manufacturing

¹⁵Mandatory reporting to FDA of serious adverse events is now required as a result of the enactment of the "Dietary Supplement and Non-Prescription Drug Consumer Protection Act" (Public Law 109-462), signed into law on December 22, 2006.

problems. If we assume that each recall is a proxy for a reported illness, then the total number of illnesses per year is approximately 1,180. We recognize that our procedure generated uncertain estimates of the number of illnesses. With a multiplier of 10, the estimated number of illnesses per year is 118; with a multiplier of 40, the total number of illnesses per year is 472.

We estimate that the monetary value of the health losses for the hazards listed in table 23 of this document as a weighted average of the values attached to the different health outcomes associated with each hazard. We estimate the health losses or fatal cases as the monetary value of a statistical life, defined as the willingness to pay for a small change in the probability of death. We estimate the health losses for non-fatal illnesses as the sum of: (1) The imputed value of lost productivity, (2) the imputed value of pain and suffering, and (3) actual expenditures on medical treatment. We measured lost productivity (defined to include household and market productivity) indirectly with measures of functional state, which includes measures of physical function. We estimated the losses caused by pain and suffering with a symptom-problem index. We combine the functional losses with the pain and suffering into a single index of lost quality-adjusted life years (measured by the Quality of Well-Being Index). We then convert the quality-adjusted life years to dollars by multiplying the index numbers by the dollar value of a quality-adjusted life year. We used direct measures of medical costs, such as payments to physicians and hospitals. We obtained data on the cost of a hospital day and other medical costs from the Health Care Cost and Utilization Project's Nationwide Inpatient Sample, administered by the HHS Agency for Healthcare Research and Quality (Ref. E14).

Table 23 of this document contains summaries of our measures of the health costs potentially caused by known instances of hazards associated with poor dietary supplement manufacturing processes for the decade 1990 through 1999. We estimated the health loss per day for the different levels of illness severity by summing the lost productivity (as measured by functional state) and the loss from pain and suffering (as measured by the symptom-problem index). These losses per day can be interpreted as the difference between a day of normal health and a day of suffering from the health conditions caused by these defective products. The numerical scale is a relative baseline that rests on the notion of a quality-adjusted life day (QALD). The QALD for a day of normal health equals 1; the QALD for death equals 0. The loss of QALDs per illness equals the daily loss multiplied by the number of days the illness lasts. We converted QALDs to dollars by multiplying the index numbers by the dollar value of a QALD. We computed the monetary value of a QALD using three values derived from three different values for a quality-adjusted life year: \$100,000, \$300,000, and \$500,000. These yield values per day of \$274, \$822, and \$1,370. Our base measures use \$822; we show the effects of using other values in the sensitivity analysis.

TABLE 23.—SUMMARY OF HEALTH EFFECTS BASED ON POTENTIAL ILLNESS ASSOCIATED WITH RECALLS BETWEEN 1990 AND 1999

	Recall Class	Number of Recalls	Expected Value of Illness	Expected Value of Illness Times Number of Recalls
Chemical				
Copper salts	2	1	\$489	\$489
Digitalis	1	33	\$37,442	\$1,235,599
Ephedra	1	1	\$177,237	\$177,237
Hypervitaminosis A	1	2	\$1,264	\$2,528
Hypervitaminosis D	2	1	\$1,366	\$1,366
Lead poisoning (class 1)	1	1	\$15,591	\$15,591
Lead poisoning (class 2)	2	40	\$10,436	\$417,451
Niacin	2	2	\$5,802	\$11,603
Pyridoxine (Vitamin B6)	2	1	\$12,085	\$12,085

TABLE 23.—SUMMARY OF HEALTH EFFECTS BASED ON POTENTIAL ILLNESS ASSOCIATED WITH RECALLS BETWEEN 1990 AND 1999—
Continued

	Recall Class	Number of Recalls	Expected Value of Illness	Expected Value of Illness Times Number of Recalls
Selenium poisoning (class 1)	1	1	\$755,338	\$755,338
Selenium poisoning (class 2)	2	6	\$1,288	\$7,731
Stannous fluoride	1	1	\$1,266	\$1,266
Superpotent zinc	2	1	\$389	\$389
Biological				
Botulism (class 1)	1	1	\$494,683	\$494,683
Botulism (class 2)	2	1	\$2,044	\$2,044
Klebsiella Pneumonia	1	1	\$774,178	\$774,178
Salmonella (class 1)	1	4	\$15,298	\$61,191
Salmonella (class 2)	2	4	\$778	\$3,110
Allergenic				
Lactose intolerance	2	1	\$396	\$396
Undeclared sulfites	1	1	\$723	\$723
Yellow #5 sensitivity	2	5	\$723	\$3,616
Yellow #6, red #40, blue #2	2	1	\$1,595	\$1,595
Physical				
Glass fragments	2	1	\$4,241	\$4,241
Other				
L-tryptophan (Eosinophilia-Myalgia Syndrome (EMS))	1	7	\$1,135	\$7,946
Total		118		\$3,992,397

The hazards that occurred between 1990 and 1999 are not necessarily the same hazards that would occur today. For example, botulism is rare and may no longer be a hazard associated with dietary supplements, but recalls involving botulism represent generic examples of adulteration that could occur with other substances in the absence of good manufacturing practices. Also, we base our cost estimates on information from 1999, so it is appropriate to estimate benefits from the same time.

(Comment 340) We received a comment that took issue with the way the recalls are counted. The comment asserts it is more appropriate to count each recall action as a separate recall, regardless of the number of different products affected.

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

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

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

We are no longer including the outbreak of EMS in our analysis of benefits. The product recalls associated with EMS occurred several years after the outbreak that we are now excluding. The continued benefit associated with

preventing EMS is associated with incorporating quality controls aimed at such hazards.

6. Benefits

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

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

Estimating the value of ensuring the quality of the dietary supplements and that they are manufactured according to their specifications is difficult in practice because we lack the necessary data on what is missing and how what is missing affects public health. Some dietary supplements have authorized health claim labeling that allows them to state their products may reduce the risk of chronic illnesses or conditions. Ensuring that those supplements are manufactured consistently according to the appropriate specifications will increase their effectiveness in reducing the risk of chronic

illnesses. In this analysis, we describe those benefits but are not able to quantify them.

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

- Reduced health costs associated with a reduced number of acute illnesses (quantified),
- Fewer product recalls (quantified), and
- Reduced health costs associated with a reduced number of chronic illnesses and conditions (not quantified).

This final rule could also enhance the benefits of the “Dietary Supplement and Non-Prescription Drug Consumer Protection Act” (Public Law 109–462), which requires mandatory reporting to FDA of serious adverse events. This final rule includes requirements that will provide the information needed to quickly and accurately conduct a sufficient traceback in the case of an adverse event. This enhanced ability to track information related to serious adverse events will increase both the accuracy and the speed of the response to such events, which may in many cases reduce the number of illnesses or deaths associated with unsafe dietary supplements.

(Comment 341) We received many comments on the estimated benefits. Although we did receive comments that stated the rule would benefit consumers by enhancing public confidence in dietary supplements, many comments state that the estimated benefits in the 2003 CGMP Proposal were overstated. In addition, one comment states that our estimates of benefits are double counted, because the outbreak of EMS was included in the measure of benefits from preventing a large catastrophic event as well as total benefits of reduction of illnesses measured by recalls. Furthermore, comments critical of the benefits state the search cost model used in the analysis is not applicable

or the benefits of reduced search costs do not exist, we lack evidence with which to base the estimate of reduced health care costs from elimination of rare catastrophic events, and recalls will not fall to zero as a result of implementing CGMPs.

(Response) We agree with the comment that benefits were overstated because of the inclusion of the outbreak of EMS. We no longer include the value of preventing that or similar outbreaks in our estimate of benefits. Although we do not agree with the comments on the applicability of the search model as a measure of benefits, the empirical difficulties associated with quantifying those benefits have led us to replace the search model with a qualitative description.

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

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

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

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

Health costs prevented = (QALY x value per QALY) + medical costs

We define QALY as the average quality-adjusted life year per illness; as explained earlier, we computed the average by weighting the quality adjusted life years lost for the probability of each health outcome by the expected frequency of that outcome.

To estimate the number of acute illnesses prevented, we started with the average number of recalls per year for the decade 1990 through 1999. The yearly averages for the decade were six class 1 recalls and seven class 2 recalls. As discussed previously, we then assumed that these recalls represented about 1 percent of all acute illnesses caused by the manufacturing problems leading

to the recalls. With that assumption, we estimated that the recalls represented about 530 acute illnesses from class 1 recalls and 650 acute illnesses from class 2 recalls.¹⁶ The illnesses used to estimate the benefits of the final rule represent a sample of acute illnesses that could occur without this final rule. We assume that the benefits computed for the average year from the decade 1990 through 1999 represent the annual average benefits we should expect in the future. We do not assume that the acute illnesses prevented in the future will be identical to those that occurred during 1990 through 1999.

TABLE 24.—HEALTH BENEFITS ESTIMATED USING RECALL DATA FROM 1990 THROUGH 1999

Estimated annual number of acute illnesses prevented (530 class 1 and 650 class 2 recalls)	1,180
Dollar estimate of average health benefit for preventing an acute illness associated with a class 1 or class 2 recall	\$33,800
Estimated dollar estimate of annual health benefits	\$40 million

The estimated benefits are indeed sensitive to the choice of years. For 2000 through 2005, there were 75 recalls: 29 class 1, 25 class 2, and 21 class 3. The annual averages for 2000 through 2005 are therefore 4.8 class 1, 4.2 class 2, and 3.5 class 3 recalls. We estimate that about 80 percent of the class 1 and class 2 recalls were related to manufacturing problems (for 1990 through 1999 over 95 percent of class 1 and class 2 recalls stemmed from manufacturing problems). With an average of 9 class 1 and class 2 recalls per year, our baseline estimate of total associated illnesses using 2000 through

¹⁶In the uncertainty analysis in section XXIV.B.11 of this document, we used a probability distribution to represent the uncertainty associated with the number of illnesses. We modeled the number of illnesses prevented for each class as the average number of recalled products plus a negative binomial distribution representing unknown cases. The negative binomial distribution estimates the number of failures (unknown cases) that will occur before some number of successes (known cases) for a given probability of success. In the negative binomial distribution, we assumed that the numbers of recalls represented reported cases and that the probability of reporting equaled 1 percent (Ref. E13). The mean estimated number of illnesses is 100 times the reported number of recalls.

2005 data is 900 (9 x 100). If this final rule prevents 80 percent of these events, then 720 illnesses will be prevented. We do not use this estimate to calculate baseline benefits for this final rule because we do not have a comparably recent estimate of costs. If the reduced number of recalls reflects increased controls in the industry, then the benefits and costs of this final rule will be lower than what we have estimated.

(Comment 342) We received comments critical of the estimates of reduced illness due to recalls. One comment points out that drugs, despite having stringent CGMP requirements, have a higher rate of recalls than dietary supplements, thus providing evidence that such requirements do not necessarily reduce recalls. Expanding on this thought, other comments state that we seem to assume that new CGMP requirements will reduce human error to zero and no more recalls will occur, which is said to be unrealistic.

Other comments express concern about the 100-fold multiplier used to estimate the costs related to recall-associated illnesses. The comment states that we, besides referencing Walker (2000) (Ref. E13 of this document (Ref. E16 in the 2003 CGMP Proposal)), provided no other information to substantiate the use of the 100-fold multiplier and therefore are being arbitrary. Any other number could be as accurate. In addition, other comments state that it is difficult to believe that the multiplier would be applicable to recalls associated with *Klebsiella pneumonia* and selenium poisoning, and L-tryptophan, because the severity of the illnesses would certainly have been associated with the highly publicized recalls; that is, they would not have gone unreported.

Some comments present recalculated benefits. One comment estimates benefits from fewer illnesses as a result of the 2003 CGMP Proposal to be \$10.9

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

(Response) We have not seen any new data or other information that would lead us to change the 100-fold multiplier for our basic estimate. We recognize that the multiplier is uncertain; different multipliers lead to different estimated numbers of illnesses and different estimated benefits. With a multiplier of 10, estimated benefits are 10 percent of our baseline; with a multiplier of 40, estimated benefits are 40 percent of our baseline. The estimated benefits of this final rule, thus, move in proportion to the assumed multiplier. We recognize this uncertainty and show how it affects the estimated benefits in the sensitivity analysis. The multiplier implicitly assumes that the more severe illnesses are more likely to be reported; the average reporting rate for all adverse events is assumed to be about 1 percent. The average

incorporates higher reporting rates for more severe illnesses, and lower reporting rates for less severe illnesses.

The comments on the severity weights for *Klebsiella pneumoniae* and ephedra did not persuade us to change these estimates. We based the estimates on the outcomes for severe events associated with these hazards. The *Klebsiella* weights come from the medical literature (Ref. E9); the ephedra weights are based on adverse events involving ephedrine alkaloids.

The comparison of drug recalls to dietary supplement recalls does not provide data that would cause us to change our analysis. The drug industry is far larger than the dietary supplement industry and any such comparison would have to account for that difference as well as other differences. Expenditures on prescription drugs exceeded \$200 billion in 2004.

(Comment 343) We received many comments regarding the use of the outbreak of EMS in 1989 as a basis for estimating health benefits from preventing a catastrophic event. The majority of the comments assert that CGMPs would not have prevented the outbreak. One comment expands this assertion by stating our claim that testing requirements would reduce the probability that contaminated ingredients would be released to the public is incorrect, because it was not known what, if any, contaminants caused the outbreak. Secondly, the comment states that our claim that complaint files would allow for fast identification of an adverse health event is also incorrect because the victims of EMS did not know the L-tryptophan was the cause of their illnesses.

Two other comments question the periodicity for a cycle of potential catastrophic events due to dietary supplements. One comment suggests a period of 70 years rather than our 30 years. The other comment does not

suggest a period but rather states that, since we have no data to support the cycle of 30 years, and we admit it is difficult to know how likely rare events are, it is possible that the total projected benefit could be zero.

Lastly, other comments state that the benefits from preventing a rare catastrophic event are double-counted. These comments state these benefits are double-counted because they are also included in the estimation of benefits from reduced recalls.

(Response) As stated previously, we are no longer including estimated benefits from preventing a rare catastrophic event in the analysis of benefits. We continue to include the benefits of preventing statistical cases of EMS in the annual health benefits, because several recalls of L-tryptophan, which could be associated with EMS took place during the 1990 through 1999 period.¹⁷

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

To estimate the direct benefits from fewer recalled adulterated dietary supplements, we estimate the number of annual recalls of dietary supplements that would be prevented by adherence to CGMP requirements in the final rule. From 1990 to 1999, FDA received reports on 195 recalls related to manufacturing problems, an average of 19.5 recalls per year (Ref. E9). The

¹⁷We recognize, however, that the presence of L-tryptophan only indicates a small probability of EMS. The estimates in table 23 of this document assume that L-tryptophan represents a 0.1 percent probability of EMS.

average figure reported here includes class 3 recalls. The number of units of dietary supplements for each recalled product varied, so we used a distribution per recall of 1,000 units to 34,000 units (Ref. E9). Product price (updated to 2004) also varies, with most prices falling between \$6 per unit and \$11 per unit; we used a most likely price of \$8.50 per unit. We include an adjustment for the goodwill lost by the establishment as a result of the recall. We multiply the direct cost of the recall by two in order to include the lost goodwill. We also adjust for recalls that would likely not be prevented by the final rule. The result is an estimated savings of \$1.8 million in direct costs and \$1.8 million in goodwill, for a total savings of about \$3.6 million per year.

(Comment 344) We received several comments on our estimates of the reduction in recalls. As noted previously, a comment generally states that drugs, despite having stringent CGMP requirements, have a higher rate of recalls than dietary supplements, thus providing evidence that CGMPs do not necessarily reduce recalls. Again, other comments state that we seem to hold the unrealistic assumption that the final rule will reduce human error to zero and no more recalls will occur. Another comment points out that the assumption that the final rule would cause the discovery of all adulteration is inconsistent with the requirement that firms keep complaint files. If the rule eliminates adulteration, the comment states, then there should be no complaints to report.

(Response) We do not believe that recalls will fall to zero. We assume that the recalls identified as being preventable by this final rule will fall to zero, but that mistakes and other hazards will continue to generate recalls. In the sensitivity analysis, however, we show the effects of a lower level of effectiveness in preventing recalls associated with manufacturing problems.

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

d. *Benefits from known nutritional effects.* Many of the nutritional benefits of vitamins and minerals are known and well-documented. For example, the Dietary Guidelines for Americans, 2005 states that dietary supplements can be used to help meet the recommended intakes of vitamin B12, folic acid, and vitamin D (Ref. E15). The Institute of Medicine's Dietary Reference Intakes include statements that supplements can be sources of several vitamins and minerals (Ref. E16). We have recognized the use of supplements in authorized health claims for calcium and osteoporosis (§ 101.72) and folic acid and neural tube defects (§ 101.79).

In table 25 of this document, we list some of the health benefits associated with the consumption of various dietary supplements.

TABLE 25. SELECTED HEALTH BENEFITS FROM CERTAIN DIETARY SUPPLEMENTS

Dietary Supplement	User	Benefit
Folic acid	Women of child-bearing age	Reduces the risk of neural tube defects
Calcium	Children and adults	Reduces the risk of osteoporosis
Iron	Adolescent females and women of child-bearing age	Reduces the risk of anemia
Vitamin D	Children and adults; persons with dark skin, or with too little exposure to sunlight	Reduces the risk of osteoporosis
Vitamin B12	Persons over the age of 50	Reduces the risk of anemia

e. *Benefits from uncertain nutritional effects.* We do not know the full range of effects (or lack of effects) of most dietary supplements. Vitamins and

minerals with known nutritional effects in supplement form may have other effects that we have yet to discover. Our uncertainty is particularly large with respect to the nutritional effects of herbal and botanical supplements. The evidence is still too mixed and incomplete to determine the effects of most of these substances. If, however, herbal dietary supplements do indeed have significant beneficial effects on the risk of chronic illnesses and conditions, then if the final rule ensures that the supplements consistently meet their specifications, we should add those benefits to those from supplements having known nutritional effects.

The benefits of this final rule that we can identify are those associated with the known effects. The product deficiency might be, for example, that packages contain some percentage less or more of the necessary ingredient (such as calcium) than what is listed on the label. The relationship between the shortage or excess amount of the ingredient and the probability of chronic illness would also have to be taken into account in order to determine the risk associated with the product deficiencies. The increase in the probability of chronic illnesses may be negligible, less than, the same, or more than the shortage or excess in the amount of the ingredient. The increase in the probability of chronic illness would also depend on how long the supplement contained a shortage or excess amount of the ingredient. Suppose, for example, that a calcium supplement contains 10 percent less calcium than it should for 1 year. If the average consumer takes calcium supplements for 20 years, would the 1-year deficiency of 10 percent increase the probability of osteoporosis by more or less than 0.5 percent (10 percent \times (1/20))?

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

estimate benefits by multiplying the additional number of chronic illnesses prevented by the value of preventing those illnesses. The values consumers place on preventing illness differ across illnesses and across consumers, and are related to the reasons they use dietary supplements. We will illustrate the method with two examples: Calcium and osteoporosis and folic acid and neural tube defects.

Calcium and osteoporosis. Many consumers take calcium supplements to reduce the probability of osteoporosis, which afflicts as many as 10 million people over age 50 (about 8 million women and 2 million men). An additional 34 million men and women may be at risk for developing osteoporosis (Ref. E17). If ensuring that calcium supplements contain what they should reduces the risk of osteoporosis, the total osteoporosis health benefits associated with the final rule will be the number of cases prevented multiplied by the health costs per case. We estimated the health costs per case as the sum of the direct medical costs, the value of functional disability, and the value of the pain and suffering associated with the illness. Cases range in severity from mild to severe. A mild case, for example, might lead to a loss of utility (measured as quality-adjusted life years—a year of life adjusted for the individual's health status) of 0.14 per year for 9 years. If we apply a discount rate of 7 percent to the years the condition lasts, the loss of quality-adjusted life years is about 0.9 (6.5 discounted years x 0.14 lost utility per year). In other rulemakings we have used a range of values for a quality-adjusted life year; the range has been from \$100,000 to \$500,000, with a medium monetary value of \$300,000 (68 FR 41434, July 11, 2003). With a value per year of \$300,000, the value of preventing a mild case is about \$270,000 (0.9 x \$300,000).

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

Folic acid and neural tube defects. Many women of child-bearing age take dietary supplements to help ensure their own health, and the health of their children should they become pregnant. For example, 40 percent of women aged 18 to 45 take supplements containing folic acid, which may reduce the probability that children will be borne with neural tube defects (Ref. E18). Neural tube defects affect the spine (spina bifida) and the brain (anencephaly). About 3,000 pregnancies are affected each year (Ref. E18).

The benefit of ensuring that folic acid supplements contain what they should equals the population at risk multiplied by the reduction in the probability of neural tube defects, multiplied by the value of preventing a neural tube defect. Neural tube defects involve large medical expenses, and either early death or permanent disability. The lifetime medical costs alone are between \$400,000 and \$500,000 for spina bifida (Ref. E19, with values updated). In recent rulemakings, we have used \$5 million as the value of a statistical life, defined as the willingness to pay for reductions in small risks of premature death. Preventing a statistical death from anencephaly would therefore generate benefits of \$5 million to \$6.5 million. For spina bifida, one estimate is that an average case leads to a loss of more than 15 quality-adjusted life years, for a monetized loss of close to \$5 million for a non-fatal case if

valued at \$300,000 per quality adjusted life year (Ref. E20). The value of preventing a case of spina bifida, then, is the sum of medical costs and the value of a saving the quality-adjusted life years, or about \$5 million (\$450 million value of quality adjusted life years + \$500,000 direct medical costs).

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

(Comment 345) We received many comments about the estimated benefits as measured by the value of hypothetical search time.

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

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

(Comment 346) One comment states that our total estimated benefits could be as little as \$21 million.

(Response) Our current estimate of total quantified benefits is \$44 million per year, once the final rule takes full effect. In addition, as discussed

previously, there are benefits to this rule that have not been quantified. The unqualified benefits estimate is the mean of a range of estimates based on assumptions about reporting rates and the effectiveness of the final rule.

In the analysis of benefits for this rule there are two large uncertainties: Quantified underreporting of acute illnesses and injuries and nonquantified benefits associated with chronic illnesses. Despite the best efforts by public health authorities, there will always be underreporting of illness and injuries. Where fatalities are concerned, unless there are litigation problems or the potential for the spread of infectious disease, there is no incentive to do extensive forensic work to determine whether a fatality is related to the ingestion of a dietary supplement. This leads to reporting most fatalities under the most general International Classification of Diseases codes. We acknowledge the large uncertainties in our estimate because of these factors.

The degree of prevention of chronic illnesses due to preventing super- or subpotent dietary supplements depends on two factors, both of which are highly uncertain. The first factor concerns product benefit: How many dietary supplements have any beneficial effect on chronic illnesses and how strong are those effects? Recent work in this area so far has examined only a few dietary supplements, with mixed results. Of course, ensuring the potency of an ingredient that has adverse effects or has adverse interactions with drugs would subtract from the benefits. The second factor is the incidence and effects of subpotency and superpotency across products and over time: How much of a difference in the product need there be to generate a substantial adverse health effect? Because of these uncertainties, it is virtually impossible to make any sort of quantitative statement about likely effects of a regulation ensuring against superpotency and subpotency.

Because of the uncertainties in estimating the benefits associated with both chronic and acute illnesses associated with manufacturing practices for dietary supplements, the decision to implement regulatory requirements becomes an exercise in weighing quantitative and qualitative benefits to public health against expenditure of scarce resources. By choosing to go forward with this rule, FDA is exercising precaution with respect to uncertain risks.

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 quantifiable benefits. Using plausible assumptions about the uncertain variables, we estimate that total quantified benefits (using 1990 through 1999 data) most likely fall within a range of \$8 million to \$64 million per year.

TABLE 26.—SUMMARY OF ANNUAL BENEFITS

Benefits	Mean
Fewer acute illnesses	\$40 million
Fewer product recalls	\$4 million
Fewer chronic illnesses	Not quantified
Total quantified benefits	\$44 million

7. Costs

The same changes in manufacturing practices that produce benefits also have opportunity costs. Due to the increased expenditures of complying with this final rule, firms may spend fewer resources on potentially costly activities such as worker safety, product development and marketing, or voluntary testing of the efficacy of their products. The final rule will require dietary supplement establishments to adopt some new practices in order to manufacture, package, label, or hold their products in compliance with CGMP requirements. In some cases, establishments will make capital improvements to the physical plant, add or replace equipment or controls, perform additional

maintenance, establish written procedures, keep records, carry out tests, monitor production and process controls, or execute a variety of additional tasks that they may not have previously performed. Not all firms will comply; some will go out of business or move their plants to other countries and not sell their product in the United States. We estimated the additional costs of production associated with the final rule and the leading regulatory options using the survey to estimate baseline manufacturing practices (Ref. E2).

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

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

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

For each size category, we constructed a cost model that included every provision of the final rule. We then attached a cost to each provision that had an additional activity associated with it. Most provisions did not have costs attached to them, because they were either descriptive or the costs were included elsewhere.

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

establishment, the number of employees, or the annual number of batches produced or affected.

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

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

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

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

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

(Comment 347) One comment states that we failed to consider start-up costs.

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

(Comment 348) Many comments on the regulatory impact analysis targeted our estimates of firms' batches per year. Nearly all comments about batches state that our batch estimates are too low. For example, an industry trade groups claims our estimate of 309 batches per year for large firms is "implausibly low." The same comment states that the distribution of the number of batches per firm of 309, 554, and 223 for large, small, and very small firms is "illogical" because it does not make sense that large firms would have fewer batches per year than small firms.

(Response) Due to a contractor's error, we used an inaccurate estimate of the annual number of batches in the analysis of the 2003 CGMP Proposal. The analysis of the final rule corrects for this error. The corrected mean numbers of batches per firm are 444 for very small, 2,436 for small, and 1,164 for large firms. The corrected estimates of the number of batches continue to show that small firms produce more batches than large firms. Comments from self-described small firms suggest that this distribution of batches is reasonable. These comments state that small firms produce many small batches of product using machinery with smaller capacity than that used by large firms. Very

small firms produce the fewest number of batches per firm of the three size categories because of their much lower output.

(Comment 349) One comment states that we used faulty data in the economic analysis.

(Response) In accordance with our information quality guidelines, we have used the best available data in this analysis. As explained in the response to comment 348, the survey results used in the analysis of the 2003 CGMP Proposal included an inaccurate estimate of the number of batches of dietary supplements produced. We use the corrected estimate in the analysis of this final rule.

(Comment 350) Some comments dispute the estimated testing costs. In particular, comments question our assumptions on:

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

(Response) The final rule reduces the number of required tests. In the final rule, we account for tests where no analytical methods have been developed. We now require fewer tests, although we anticipate that some testing will take place associated with the creation of certificates of analysis required for component specifications and as verification for process controls. We now assume that the tests will be:

- One identity test for each shipment lot of incoming dietary ingredients (e.g., vitamin C);
- Tests of subsets of shipment lots by supplier firms to create certificates of analysis for identity of other components (e.g., sugar);