

use in the manufacture of a dietary supplement, and release them from quarantine.

Final § 111.155 modifies proposed § 111.40(a)(3) which would require:

- You to quarantine components until your quality control unit reviews the supplier's invoice, guarantee, or certification;
- The quality control unit to perform testing, as needed, of a representative sample to determine that specifications are met;
- You to conduct a material review and make a disposition decision if specifications are not met; and
- The quality control unit to approve and release the components from quarantine before you use them.

Final § 111.155(c) includes revisions related to the following changes to other provisions already discussed.

- Under final § 111.110, quality control personnel ensure that all appropriate tests and examinations are conducted, and review and approve the results of tests and examinations conducted on components, but quality control personnel are not required to conduct the tests or examinations;
- Under final § 111.80(a), we establish the convention in this final rule of referring to “each unique lot within each unique shipment” rather than “each shipment lot;”
- The requirements to conduct a material review and make a disposition decision are already set forth in final §§ 111.87, 111.113, and 111.120 and, therefore, are not repeated in final § 111.155; and
- Under final § 111.90(c), any batch of dietary supplement that is reprocessed, that contains components that you have treated, or to which you have made in-process adjustments to make them suitable for use in the manufacture of the dietary supplement, must meet all product specifications

for the dietary supplement and be approved by quality control personnel before being released for distribution.

(Comment 243) Some comments address the requirement to quarantine components before you use them and assert that it is not feasible to quarantine incoming materials in a continuous extraction and purification operation, such as one built adjacent to a soy crushing or vegetable oil refinery to receive a continuous side stream flow from that operation. One comment explains that in such operations, quarantine and quality control approval occurs later in the process after the material has been isolated and concentrated in a stable matrix suitable for holding. One comment suggests proposed § 111.40(a)(3) state “quarantine components or dietary supplements as applicable * * *”.

(Response) We decline to revise proposed § 111.40(a)(3) as suggested by the comments. The comment describes a situation where a manufacturer of a dietary supplement is also manufacturing a dietary ingredient or other component but only provides limited information. It appears that, however, the procedures described for quarantine of the isolated, stable matrix, with subsequent evaluation by quality control personnel before release for use in the manufacture of the dietary supplement, would satisfy the requirements of final § 111.155(c), provided quality control personnel are able to determine that all specifications for the component are met.

(Comment 244) One comment states that plant personnel who are not formally part of the manufacturer’s quality control unit can conduct the quality control functions required for the release of materials from quarantine before use.

(Response) As already discussed with respect to the definition of quality control personnel (see section VI of this document), these comments may have

misunderstood the role of the quality control unit (now quality control personnel). To clarify that role, final § 111.12(b) states you must identify a qualified person who is responsible for your quality control operations.

(Comment 245) One comment suggests components that cannot be used in a short time should be retested at least yearly.

(Response) We are making no changes to the provision after considering this comment. Whether any tests or examinations must be repeated over time, or whether the information in a certificate of analysis remains valid over time, is a matter to be decided by the manufacturer based on the established characteristics and shelf life of the component.

5. Final § 111.155(d)

Final § 111.155(d)(1) (proposed § 111.40(a)(4)) requires you to identify each unique lot within each unique shipment of components you receive and any lot of components that you produce in a manner that allows you to trace the lot to the supplier, the date received, the name of the component, the status of the component (e.g., quarantined, approved, or rejected), and to the dietary supplement you manufactured and distributed. Final § 111.155(d)(2) requires you to use this unique identifier whenever you record the disposition of each unique lot within each unique shipment of components that you receive and any lot of components that you produce.

Final § 111.155(d)(1) and (d)(2) are substantially similar to proposed § 111.40(a)(4) which would require you to identify each lot of components in a shipment in a manner that allows you to trace the shipment to the supplier, the date received, the name of the component, and the status (e.g., quarantined, approved, or rejected), and to trace the shipment lot to the dietary supplement you manufactured and distributed. Proposed § 111.40(a)(4) also would require

you to use this unique identifier whenever you record the disposition of each shipment lot received.

Final § 111.155(d)(1) and (d)(2) include revisions associated with final § 111.80(a).

We did not receive comments specific to proposed § 111.40(a)(4).

6. Final § 111.155(e)

Final § 111.155(e) (proposed § 111.40(a)(5)) requires you to hold components under conditions that will protect against contamination and deterioration and avoid mixups.

We did not receive comments specific to proposed § 111.40(a)(5).

F. What Requirements Apply to Packaging and Labels Received? (Final § 111.160)

1. Final § 111.160(a)

Final § 111.160(a) (proposed § 111.40(b)(1)) requires you to visually examine each immediate container or grouping of immediate containers in a shipment for appropriate content label, container damage, or broken seals to determine whether the container condition may have resulted in contamination or deterioration of the packaging and labels. Final § 111.160(a) is similar to proposed § 111.40(b)(1) with the addition of the word “immediate” to identify the container as the container that is in contact with the packaging or labels and substituting “may have” for “has” before the word “resulted” as discussed in this section.

We did not receive comments specific to proposed § 111.40(b)(1).

2. Final § 111.160(b)

Final § 111.160(b) requires you to visually examine the supplier's invoice, guarantee, or certification in a shipment to ensure the packaging or labels are consistent with your purchase order. Final § 111.160(b) is a new requirement that is analogous to proposed § 111.40(a)(2). We are requiring in final § 111.160(b), that, as part of your visual identification, you compare what was received, based on the supplier's invoice, guarantee, or certification, with your purchase order so you can ensure your specifications for packaging and labels are met. This is consistent with what you would do with respect to components and dietary supplements you receive. Without final § 111.160(b), the review by quality control personnel under final § 111.120(a) would be a matter of performing receiving operations rather than performing quality control operations; as already discussed in this section, some comments asserted the quality control unit should focus on reviewing the work of others rather than conducting the operations themselves. Thus, final § 111.160 is consistent with these comments.

3. Final § 111.160(c)

Final § 111.160(c) requires you to quarantine packaging and labels before you use them in the manufacture of a dietary supplement until:

- You collect representative samples of each unique shipment, and of each unique lot within each unique shipment, of packaging and labels and, at a minimum, conduct a visual identification of the immediate containers and closures;
- Quality control personnel review and approve the results of any tests or examinations conducted on the packaging and labels; and

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

Final § 111.160(c) is similar to proposed § 111.40(b)(2) which would require that:

- You quarantine packaging and labels until your quality control unit tests or examines a representative sample to determine that specifications are met;
- You conduct at least a visual identification of the containers and closures;
- If specifications are not met, you conduct a material review and make a disposition decision; and
- Your quality control unit approve and release packaging and labels from quarantine before you use them.

Final § 111.160(c) includes revisions that reflect the following change already discussed in this final rule:

- Refers to “each unique lot within each unique shipment” rather than “each shipment lot”.

We did not receive comments specific to proposed § 111.40(b)(2).

4. Final § 111.160(d)

Final § 111.160(d)(1) requires you to identify each unique lot within each unique shipment of packaging and labels in a manner that allows you to trace the lot to the supplier, the date received, the name of the packaging and label, the status of the packaging and label (e.g., quarantined, approved, or rejected), and to the dietary supplement you distributed. Final § 111.160(d)(2) requires you to use this unique identifier whenever you record the disposition of each unique lot within each unique shipment of packaging and labels. Final § 111.160(d) derives from proposed § 111.40(b)(3) which would require you to

identify each shipment lot of packaging and labels in a manner that allows you to trace the shipment lot to the supplier, the date received, the name of the packaging and label and the status (e.g., quarantined, approved, or rejected) and to trace the shipment lot to the dietary supplement manufactured and distributed. Proposed § 111.40(b)(3) also would require that you use this unique identifier whenever you record the disposition of each shipment lot received.

Final § 111.160(d) includes revisions that reflect the following changes already discussed in this final rule:

- Reference to “each unique lot within each unique shipment” rather than “each shipment lot.”
- As a clarification, final § 111.160(d)(2) refers to the “dietary supplement that you distributed” rather than to the “dietary supplement manufactured and distributed” to avoid a narrow—and incorrect—interpretation of “manufactured.” Under proposed § 111.40(b)(3), we used the term “manufactured” in a broad sense that includes any aspect of the manufacturing process rather than a narrow sense that applied to manufacturing operations for producing a batch of dietary supplement. Both proposed § 111.40(b)(3) and final § 111.160(e) address the need to trace the packaging and labels that you use to the product that you distribute, regardless of whether your role in the manufacturing process includes the production of the batch or includes only packaging a dietary supplement you receive from a supplier.

(Comment 246) One comment believes packaging and labels are rarely the source of quality problems. This comment suggests proposed § 111.40(b)(3) allow the use of packaging approved by the quality control unit without the need to use a specific lot identification number. The comment explains that

this type of flexibility is needed when they have dozens of short run lots each day and use less than a carton of packaging supplies for each run.

(Response) This comment may have misinterpreted proposed § 111.40(b)(3). Under proposed § 111.40(b)(3) (final § 111.160(d)) you must assign the identifier to each unique lot within each unique shipment of packaging and labels when you receive them rather than each time that you use them. This number would stay the same for each of the short runs described by the comment. We are making no changes to the requirement.

5. Final § 111.160(e)

Final § 111.160(e) requires you to hold packaging and labels under conditions that will protect against contamination and deterioration, and avoid mixups. Final § 111.160(e) is identical to proposed § 111.40(b)(4).

We did not receive comments specific to proposed § 111.40(b)(4).

G. What Requirements Apply to a Product Received for Packaging or Labeling as a Dietary Supplement (and for distribution rather than for return to the supplier)? (Final § 111.165)

Final § 111.165 (proposed § 111.40(a)) sets out actions you must take when you receive a product for packaging and labeling and for distribution. Final § 111.165 includes editorial changes associated with the reorganization and revisions that reflect changes we are making to other sections of the final rule.

Final § 111.165 sets forth requirements for “product that you receive from a supplier for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier)” rather than for “dietary supplements that you receive.”

The final rule separates the requirements in proposed § 111.40(a) for product that you receive from a supplier for packaging or labeling as a dietary

supplement (and for distribution rather than for return to the supplier) (final § 111.165) from the analogous requirements for components, packaging, and labels (final § 111.155).

1. Final § 111.165(a)

Final § 111.165(a) requires you to visually examine each immediate container or grouping of immediate containers in a shipment of product you receive for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier) for appropriate content label, container damage, or broken seals to determine whether the container condition may have resulted in contamination or deterioration of the received product. Final § 111.165(a) is substantially similar to proposed § 111.40(a)(1) which, in part, would impose this requirement for dietary supplements you receive. We have added the word “immediate” to identify the container as the container that is in contact with the product you receive for packaging or labeling as a dietary supplement and substituted “may have” for “has” before the word “resulted” as explained in this section.

2. Final § 111.165(b)

Final § 111.165(b) requires you to visually examine the supplier’s invoice, guarantee, or certification in a shipment of the received product to ensure the received product is consistent with your purchase order. Final § 111.165(b) is substantially similar to proposed § 111.40(a)(2) which, in part, would establish a similar requirement for dietary supplements that you receive.

3. Final § 111.165(c)

Final § 111.165(c) requires you to quarantine the received product until:

- You collect representative samples of each unique shipment, and of each unique lot within each unique shipment, of received product;
- Quality control personnel review and approve the documentation to determine whether the received product meets the specifications that you established under § 111.70(f); and
- Quality control personnel approve the received product for packaging or labeling as a dietary supplement and release the received product from quarantine.

Final § 111.165(c) is similar to proposed § 111.40(a)(3) which, in part, would require that:

- You quarantine dietary supplements that you receive until your quality control unit reviews the suppliers invoice, guarantee, or certification;
- The quality control unit performs testing, as needed, of a representative sample to determine that specifications are met;
- You conduct a material review and make a disposition decision if specifications are not met; and
- The quality control unit approves and releases the dietary supplements that you receive from quarantine before you use them.

Final § 111.165(c) includes revisions that reflect that under final § 111.75(e) before you package or label a product you received for packaging or labeling as a dietary supplement, you must visually examine the product and have documentation to determine whether the specifications you established under § 111.70(f) are met, but not otherwise examine or conduct tests.

4. Final § 111.165(d)

Final § 111.165(d)(1) requires that you identify each unique lot within each unique shipment of received product in a manner that allows you to trace the lot to the supplier, the date received, the name of the received product, the status of the received product (e.g., quarantined, approved, or rejected), and to the product you packaged or labeled and distributed as a dietary supplement. Final § 111.165(d)(2) requires you to use this unique identifier whenever you record the disposition of each unique lot within each unique shipment of the received product. Final § 111.165(d) derives from proposed § 111.40(a)(4) which would require you, in part, to identify each lot of dietary supplements in a shipment in a manner that allows you to trace the shipment to the supplier, the date received, the name of the dietary supplement, and the status (e.g., quarantined, approved, or rejected), and to trace the shipment lot to the dietary supplement manufactured and distributed. Proposed § 111.40(a)(4) also would require you to use this identifier whenever you record the disposition of each shipment lot received.

Final § 111.165(d) includes a revision associated with final § 111.80 referring to “each unique lot within each unique shipment” rather than “each shipment lot.”

5. Final § 111.165(e)

Final § 111.165(e) requires you to hold the received product under conditions that will protect against contamination and deterioration, and avoid mixups. Final § 111.165(e) derives from proposed § 111.40(a)(5) with editorial changes associated with the reorganization.

H. What Requirements Apply to Rejected Components, Packaging, and Labels, and to Rejected Products That Are Received for Packaging or Labeling as a Dietary Supplement? (Final § 111.170)

Final § 111.170 requires you to clearly identify, hold, and control under a quarantine system for appropriate disposition any component, packaging, and label, and any product you receive for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier), that is rejected and unsuitable for use in manufacturing, packaging, or labeling operations. Final § 111.170 is substantially similar to proposed § 111.74 which would require you to clearly identify, hold, and control under a quarantine system any component, dietary supplement, packaging, and label that is rejected and unsuitable for use in manufacturing, packaging, or labeling operations.

We did not receive comments specific to proposed § 111.74. Final § 111.170 includes revisions associated with the series of provisions that distinguish a product you receive for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier) from a dietary supplement you manufacture.

I. Under This Subpart, What Records Must You Make and Keep? (Final § 111.180)

Final § 111.180 sets forth the requirements to make and keep records associated with components, packaging, labels, and product you receive for packaging and labeling as a dietary supplement. Final § 111.180 derives from proposed § 111.40(c).

1. Final § 111.180(a)

Final § 111.180(a) requires you to make and keep records required under subpart G in accordance with subpart P. Final § 111.180(a) derives from proposed § 111.40(c)(2), with editorial changes associated with the reorganization.

We did not receive comments specific to the requirements set forth in final § 111.180(a).

2. Final § 111.180(b)(1)

Final § 111.153 requires you to establish and follow written procedures to fulfill the requirements of subpart G. These written procedures are records. Therefore, final § 111.180(b)(1) requires you to make and keep a record of the written procedures for fulfilling the requirements of subpart G.

3. Final § 111.180(b)(2)

Final § 111.180(b)(2) requires you to make and keep receiving records (including records such as certificates of analysis, suppliers' invoices, and suppliers' guarantees) for components, packaging, and labels, and for products you receive for packaging or labeling as dietary supplements (and for distribution rather than for return to the supplier). Final § 111.180(b)(2) derives from proposed § 111.40(c)(2) with editorial changes associated with the reorganization. Final § 111.180(b)(2) also includes revisions associated with the series of provisions that distinguish a product you receive for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier) from a dietary supplement you manufacture. Because the final rule provides that you may rely, under certain circumstances, on a certificate of analysis to ensure that some component specifications are met (final § 111.75(a)(2)(ii)) and that you may rely, in part, on documentation to

determine whether specifications for received products are met, we specifically identify a certificate of analysis and common forms of documentation as being “receiving records” for purposes of this rule.

(Comment 247) One comment on proposed § 111.40(c)(2) points out the recordkeeping requirements of any final rule will be a costly burden for a company that produces multiple ingredient products in several packaging configurations and will be much greater than the burden for a company that produces batches of single ingredient products in one packaging configuration.

(Response) We acknowledge that companies that produce multiple ingredient products in several packaging configurations will have more records to keep than companies that produce single ingredient products in one packaging configuration. However, these records are necessary to be able to determine the source of the component, packaging, and labels, so that if adulteration of the dietary supplement occurs, the records will show the source of the material so that its use can be stopped.

4. Final § 111.180(b)(3)

Final § 111.180(b)(3) requires you to make and keep documentation that the requirements of subpart G were met. Under final § 111.180(b)(3)(i), the person who performs the required activity must document, at the time of performance, that the required operation was performed. Under final § 111.180(b)(3)(ii), the documentation must include:

- The date that the components, packaging, labels, or products you receive for packaging or labeling as a dietary supplement were received;
- The initials of the person performing the required operation;

- The results of any tests or examinations conducted on components, packaging, or labels, and of any visual examination of product you receive for packaging or labeling as a dietary supplement; and
- Any material review and disposition decision conducted on components, packaging, labels, or products that you receive for packaging or labeling as a dietary supplement.

Final § 111.180(b)(3) differs from proposed § 111.40(c)(1)(i) through (c)(1)(iv), by referring to “required operation” rather than “requirement.” Additionally as a conforming revision associated with final § 111.75(a) which requires appropriate tests and examinations, final § 111.180(b)(3) requires you to include in the documentation the results of any examinations as well as tests. Final § 111.180(b)(3) also includes revisions associated with the series of changes that distinguish a product that you receive for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier) from a dietary supplement that you manufacture.

(Comment 248) A few comments note proposed § 111.40(c) requires the signature of the person performing the requirement, whereas other sections of the 2003 CGMP Proposal, such as proposed § 111.50(c)(2), only require the initials of the person performing the requirement. One comment requests the format for the requirement to document the person performing the step be made consistent throughout the regulations.

(Response) We agree that the identity of the person performing a requirement should be required throughout the final rule and that this can be accomplished through initials except for operations that are performed by quality control personnel. Therefore, we are revising the requirements so that a signature (and not initials) is required for any operation performed by quality

control personnel (see final § 111.140). Because § 111.40(c)(1)(ii) is not a quality control operation, we also revised proposed § 111.40(c)(1)(ii) (final § 111.180(b)(3)) to require the initials, rather than the signature, of the person performing the required operation. Initials are required for other circumstances that do not involve quality control operations, including final § 111.180(b)(3). However, whenever this final rule requires initials, a signature is also acceptable, because a signature would achieve the goal of identifying the person who performed the requirement.

XIII. Comments on the Production and Process Control System: Requirements for the Master Manufacturing Record (Final Subpart H)

A. Organization of Final Subpart H

In the 2003 CGMP Proposal, the requirements for the master manufacturing record were set forth in proposed § 111.45. As shown in table 9 of this document, we are setting forth the requirements for the master manufacturing record in a distinct subpart (final Subpart H—Production and Process Control System: Requirements for the Master Manufacturing Record). Table 9 lists the sections in final subpart H and identifies the proposed provisions that form the basis for the final rule.

TABLE 9.—DERIVATION OF SECTIONS IN FINAL SUBPART H

Final Rule	2003 CGMP Proposal
§ 111.205 What is the requirement to establish a master manufacturing record?	§ 111.45(a)(1), (a)(2), and (d)
§ 111.210 What must the master manufacturing record include?	§ 111.45(b)

The requirements in final subpart H are set forth from the perspective of the manufacture of a batch of a dietary supplement. You must comply with all requirements that pertain to your activity. However, you must comply with

the requirement to prepare and follow a “master manufacturing record” regardless of whether you manufacture a batch, or whether you package or label product you receive from a supplier for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier). If you are a packager or labeler, you only need to include those parts relevant to your process. For example, if you are a labeler, under final § 111.210(c) you would not need to include an accurate statement of the weight or measure of each component to be used because you would be starting from packages already filled.

B. Highlights of Changes to the Proposed Requirements for the Master Manufacturing Record

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;
- Includes revisions so the requirements for the master manufacturing record are consistent with final § 111.70(a) which requires you to establish a specification for any point, step, or stage in the manufacturing process where control is necessary to ensure the quality of the dietary supplement and that the dietary supplement is packaged and labeled as specified in the master manufacturing record; and
- Includes a revision associated with final § 111.75(h), which provides for the use of either tests or examinations for complying with the requirements of part 111.

2. Changes Associated With the Reorganization

The proposed requirement (§ 111.45(c)) that the quality control unit approve each master manufacturing record and any modifications to a master manufacturing record is set forth as final § 111.123(a) in subpart F, rather than in final subpart H, with the changes we made to the definition of “quality control unit” to “quality control personnel” as explained in section VI of this document (subpart A).

3. Changes After Considering Comments

The final rule:

- Retains a requirement to state any intentional overage of a dietary ingredient but does not require an explanation for such an overage;
- Provides flexibility to include either a representative label, or a cross-reference to the physical location of the actual or representative label if an actual label is not provided; and
- Provides flexibility for what must be included in written instructions when operations are not conducted manually.

C. General Comments on Proposed § 111.45 (Final Subpart H)

1. Comments on Written Procedures

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. As discussed in section IV of this document, we do not require you to establish and follow written procedures for preparing a master manufacturing record.

2. Comments That Support Proposed § 111.45

(Comment 249) A few comments support the proposed requirements for the master manufacturing record. One comment states that properly recorded quality control measures, such as the batch production and master manufacturing records, will aid manufacturers in producing dietary supplements in a consistent and uniform manner, as well as serve as tools to assess possible sources of contamination and flaws in the production process. Another comment asserts the master manufacturing and batch production records probably have the second greatest impact on overall product quality, surpassed only by the quality of the “people” manufacturing the product.

(Response) We agree the master manufacturing record requirements in the 2003 CGMP Proposal are important for reasons that include those expressed in the comments. Establishing a master manufacturing record will help to ensure the quality of the dietary supplement. The proposed requirements for the master manufacturing record have been codified as subpart H in this final rule.

D. What Is the Requirement to Establish a Master Manufacturing Record? (Final § 111.205)

Final § 111.205 (proposed § 111.45(a) and (d)) sets forth the requirement to prepare and follow a written master manufacturing record.

1. Final § 111.205(a)

Final § 111.205(a) requires you to prepare and follow a written master manufacturing record for each unique formulation of dietary supplement that you manufacture, and for each batch size, to ensure uniformity in the finished batch from batch to batch. Final § 111.205(a) is similar to proposed § 111.45(a)

which would require you to prepare and follow a written master manufacturing record for each type of dietary supplement you manufacture and for each batch size to ensure uniformity from batch to batch.

(Comment 250) Some comments suggest the phrase “to ensure uniformity from batch to batch” be changed to “to ensure that specifications are met from batch to batch.” One comment states the term “uniformity” could be interpreted to mean that two batches would be exactly the same, down to the minutest detail. The comment expresses concern about how batches of herbal products will meet this standard of “uniformity” from batch to batch.

(Response) These comments may have misinterpreted the term “uniformity” as we used it in proposed § 111.45(a). Uniformity means that the specifications you establish for identity, purity, strength, and composition of the finished batch must be the same throughout a given batch, e.g., at the beginning, middle, and end of a production run. To emphasize this, we have revised the requirement so it is clear that the uniformity relates to “the finished batch.” Whether two batches must be exactly the same, down to the minutest level, would depend on the specifications the manufacturer establishes for the finished batch under final § 111.70(e). Although a finished batch must meet those specifications “from batch to batch,” it is up to the manufacturer to determine what those specifications will be. We are making no changes to the requirement.

(Comment 251) Some comments assert that the proposed requirement to prepare a separate record “for each batch size” is burdensome, particularly for smaller firms who specialize in custom blended products. These comments would revise the rule so the master manufacturing record includes a master formula with instructions for how to adjust the amount of ingredients to add

depending on the batch size, with the actual amounts included in the applicable batch record.

(Response) We disagree with these comments. Requiring a separate master manufacturing record for each batch size will lessen the likelihood of mistakes that can happen when a formula is “multiplied up” or “divided down,” particularly in light of the requirement that quality control personnel review and approve each master manufacturing record (final § 111.123(a)). Moreover, it is not clear that the scenario described in the comments would lessen any burden, because a new “formula,” based on the master formula, would still need to be prepared for each batch.

In essence, these comments suggest shifting the burden from a requirement to prepare a master manufacturing record to a requirement to prepare a batch record. Under final § 111.123, quality control personnel review the master manufacturing record before that record is used, but review the batch record only after the batch is prepared. Shifting the requirement in the manner suggested by these comments would defeat the purpose of having quality control personnel review and approve each “formula.” We are not making the suggested changes to proposed § 111.45(a).

We are changing the word “type” to “unique formulation” to clarify that the requirement for a master manufacturing record applies to each different dietary supplement whether it is a different strength, includes any different ingredients, is a capsule or tablet, or includes minor variations.

2. Final § 111.205(b)(1)

Final § 111.205(b)(1) requires that the master manufacturing record identify specifications for each point, step, or stage in the manufacturing process where control is necessary to ensure the quality of the dietary

supplement and that the dietary supplement is packaged and labeled as specified in the master manufacturing record. Final § 111.205(b)(1) derives from proposed § 111.45(a)(1). We received no comments specific to proposed § 111.45(a)(1). We revised this section to include changes that we made to § 111.70(a).

3. Final § 111.205(b)(2)

Final § 111.205(b)(2) requires that the master manufacturing record establish controls and procedures to ensure that each batch of dietary supplement you manufacture meets the specifications identified in accordance with § 111.205(b)(1). Final § 111.205(b)(2) derives from proposed § 111.45(a)(2) with grammatical changes and changes associated with the reorganization. We did not receive comments specific to proposed § 111.45(a)(2).

4. Final § 111.205(c)

Final § 111.205(c) requires you to make and keep master manufacturing records in accordance with subpart P. Final § 111.205(c) derives from proposed § 111.45(a) and (d), and clarifies that you must prepare and keep the master manufacturing records. We did not receive comments specific to proposed § 111.45(d), and comments relevant to § 111.45(a) are discussed in the response to comment 250.

E. What Must the Master Manufacturing Record Include? (Final § 111.210)

Final § 111.210 sets forth the requirements for what the master manufacturing record must include. Final § 111.210 derives from proposed § 111.45(b).

1. Final § 111.210(a)

Final § 111.210(a) requires that the master manufacturing record include the name of the dietary supplement to be manufactured and the strength, concentration, weight, or measure of each dietary ingredient for each batch size. Final § 111.210(a) derives from proposed § 111.45(b)(1).

(Comment 252) One comment supports listing the weight or measure for each ingredient but believes that including the strength and concentration is unnecessary. This comment also suggests that the identity of each ingredient can be controlled using a unique item number identifier, along with a brief description of the ingredient.

(Response) Proposed § 111.45(b)(1) would require the master manufacturing record to include strength, concentration, weight, or measure of each dietary ingredient for each batch size. We did not intend that all would be required. The purpose of this requirement is to ensure the correct dietary ingredient and amount are used in a given batch. To the extent that weight or measure best describes what that dietary ingredient is and how much is to be used in a given batch, the manufacturer could use weight or measure. To the extent that a manufacturer determines, for a particular dietary ingredient, strength, or concentration would best describe what is to be used in a given batch, the manufacturer could use those instead. We are giving firms the flexibility to use the measure that they determine best describes the amount of dietary ingredient to use in their batch. For example, assume you are manufacturing a million tablets of a vitamin C product in 250 mg tablets and the only other ingredients in your product are starch, microcrystalline cellulose, and dicalcium phosphate. Under proposed § 111.45(b)(1) (final § 111.210(a)) your master manufacturing record would state: "Vitamin C 250

mg, 1,000,000 tablets.” As another example, if you are manufacturing 100 liters of a liquid dietary supplement that provides tuna oil as a dietary ingredient, and the only other ingredients are alpha-tocopherols for use as an antioxidant, then your master manufacturing record would state: “Tuna oil, 100 liters.”

The unique identifier comment states “the identity of each dietary ingredient can be controlled instead with the use of a unique item identifier, along with a brief description of the ingredient.” It is not clear what the comment meant by “a brief description of the ingredient.” If the “brief description of the ingredient” includes the identity, then it would comply with the final rule. Firms are free to use unique identifiers in addition to the identity. If, however, the comment means something other than identity, the comment fails to explain how the identity will be controlled to prevent manufacturing errors. In the absence of such an explanation, we have no basis to make the requested change.

Moreover, under final § 111.205(c) the master manufacturing record is a record you must make and keep in accordance with final § 111.610 in final subpart P. Under final § 111.610, the master manufacturing record must be available during the record retention period for inspection and copying by us when we request that you do so. A master manufacturing record that does not identify the dietary ingredient and the weight or measure of the dietary ingredient would not allow an FDA investigator to determine, for example, how your master manufacturing record relates to the finished dietary supplement and to the product label of that dietary supplement.

(Comment 253) One comment recommends the weight or measure be expressed per unit or portion, or per unit of weight or measure of the product, for each batch size.

(Response) The final rule does not prescribe the units you must use. Thus, firms have the flexibility to include this information in the way that best suits their product.

2. Final § 111.210(b)

Final § 111.210(b) requires that the master manufacturing record include a complete list of components to be used. Final § 111.210(b) is identical to proposed § 111.45(b)(2). We did not receive comments specific to proposed § 111.45(b)(2).

3. Final § 111.210(c)

Final § 111.210(c) requires that the master manufacturing record include an accurate statement of the weight or measure of each component to be used. Final § 111.210(c) is identical to proposed § 111.45(b)(3). We did not receive comments specific to proposed § 111.45(b)(3).

4. Final § 111.210(d)

Final § 111.210(d) requires that the master manufacturing record include the identity and weight or measure of each dietary ingredient that will be declared on the Supplement Facts label and the identity of each ingredient that will be declared on the ingredients list of the dietary supplement. Final § 111.210(d) is similar to proposed § 111.45(b)(4). We have removed the phrase “in compliance with section 403(s) of the act” as it is unnecessary in the context of compliance with the dietary supplement CGMP requirements. The manufacturer must still comply with section 403(s) and failure to do so will result in a misbranding violation, not a CGMP violation under this final rule.

(Comment 254) One comment supports having the identity and weight or measure of each dietary ingredient as required by proposed § 111.45(b)(4), but

asserts it is unnecessary for the verbiage to identically match the corresponding label statements. This comment also asserts that the ingredients can be controlled in the master manufacturing record by use of a unique identifier, instead of the ingredient name, along with a brief description of the ingredient.

(Response) We disagree for the reasons stated in response to comment 252 and decline to revise the provision in this manner.

5. Final § 111.210(e)

Final § 111.210(e) requires that the master manufacturing record include a statement of any intentional overage amount of a dietary ingredient. Final § 111.210(e) derives from proposed § 111.45(b)(5) which would require you to explain any intentional excess amount of a dietary ingredient.

(Comment 255) Some comments request us to modify this requirement. Several comments note that a manufacturer may design products with overage levels adjusted so the product always tests at least 100 percent of the amount claimed on the label throughout the declared shelf life. One comment states it should be sufficient to identify any overage amount, rather than having to explain it.

(Response) We understand that some firms design products using an additional amount of certain ingredients to ensure the product meets its specifications for the amount of the ingredient during the expected shelf life of the product. We agree it is not necessary to include the reason for adding the intentional excess amount.

We also understand it would be more appropriate to refer to the additional amount as an “overage” amount rather than an “excess” amount, because “overage” is commonly used in the industry to convey the practice that is now the subject of final § 111.260(e). Therefore, we have revised proposed

§ 111.45(b)(1) to use the term “overage” rather than “excess” and to delete the proposed requirement to include the reason for the intended overage. As discussed in the preamble to the 2003 CGMP Proposal (68 FR 12157 at 12203), the amount of overage should be limited to the amount needed to meet the amounts listed in accordance with final § 111.210(d).

6. Final § 111.210(f)

Final § 111.210(f) requires that the master manufacturing record include a statement of theoretical yield of a manufactured dietary supplement expected at each point, step, or stage of the manufacturing process where control is needed to ensure the quality of the dietary supplement, and the expected yield when you finish manufacturing the dietary supplement, including the maximum and minimum percentages of theoretical yield beyond which a deviation investigation of a batch is necessary and material review is conducted and disposition decision is made. Final § 111.210(f) derives from proposed § 111.45(b)(6). We revised the section to state “beyond which a deviation investigation of a batch is necessary” rather than “beyond which a deviation is performed” for clarity.

(Comment 256) One comment suggests the term “maximum and minimum percentages” in proposed § 111.45(b)(6) be replaced with the term “normal range.”

Another comment recommends proposed § 111.45(b)(6) be replaced with: “A statement of theoretical yield of a manufactured dietary ingredient or dietary supplement expected at appropriate phases of manufacturing.” This comment states the detail in this proposed requirement should be eliminated because the manufacturer should decide where and when to include a statement about theoretical yield.

(Response) Final § 111.210(f) clearly communicates when it is necessary to conduct a material review and make a disposition decision. The comment's suggestions do not improve the communication or clarify this point.

Final § 111.210(f) gives firms the flexibility to decide what steps, in the manufacturing process, are points, steps, or stages where control is needed to ensure the quality of the dietary supplement. A statement about theoretical yield is necessary at each such point, step, or stage including at the finished batch stage so that you will know, when you manufacture a batch, whether the process is proceeding as expected or whether something is wrong. For example, your master manufacturing record could state the theoretical yield after mixing a series of components is 100 percent, because nothing about the additional step would remove any material from the production system. When manufacturing the batch, a yield of less than 100 percent would tell you something was wrong, for example, if there was an obstruction that prevented a component that was being delivered by automated equipment from actually entering the production vessel. For a process such as recrystallization, knowing the theoretical yield is critical, because if the expected yield is not achieved at a given step it may mean that the process did not proceed as intended.

(Comment 257) One comment argues it is not possible for the majority of supplement products, especially botanicals, to provide 100 percent of the claimed amount of the botanical, because botanicals are inherently of uneven consistency, density, and particle size. This comment recommends that we allow for variability in yield, especially for botanicals.

(Response) Final § 111.210(f) does not specify what the yield must be, so no revision is necessary. It is the manufacturer's responsibility to manufacture the product in a way that will ensure that a product contains what the

manufacturer has established in its specifications and its master manufacturing record. The manufacturer must establish specifications for the identity, purity, strength, and composition and limits on contamination and other specifications the manufacturer decides are necessary to ensure the quality of the dietary supplements that it makes, and design and implement a production and process control system that will ensure those specifications are met. In the situation described by the comment, it is the manufacturer's responsibility to design and implement a production and process control system that will ensure the quality of the dietary supplement regardless of the problems presented by the nature of the ingredients.

7. Final § 111.210(g)

Final § 111.210(g) requires that the master manufacturing record include a description of packaging and a representative label, or a cross-reference to the physical location of the actual or representative label. Final § 111.210(g) derives from proposed § 111.45(b)(7), which would require a description of packaging and a copy of the label to be used.

(Comment 258) One comment supports the proposed requirement that the master manufacturing record contain a copy of the dietary supplement label. Other comments contend that the proposed requirement to include a copy of the label is neither appropriate nor necessary. Some comments state that companies often do not have a label available to include in the master manufacturing record and believe that a description of the packaging or label in the master manufacturing record should be sufficient. Another comment, by a company that produces many different brands for each bulk product, asserts that updating labels in the record would be burdensome and suggests wording similar to that used by USP, for which a positive identification of

all labeling used is permitted. One comment asks whether the packaging and label copy requirements can be in separate documents cross-referenced in the master manufacturing record, because some companies treat tablet manufacturing and packaging as two separate and distinct operational elements. This comment explains that the master manufacturing record includes the specifics required to manufacture the tablets, but the actual description of packaging and label copy requirements are contained in separate documents cross-referenced to the master manufacturing record by a product part number.

(Response) We understand there may be some circumstances where it would be impractical to have actual copies of labels in the master manufacturing record. If an actual label is not available, you may include a representative label in the master manufacturing record. A representative label could be a graphic representation of the label, including the exact statements that would be on the product label, or a detailed description of the statements and other information (such as pictures or graphics) that will be on the actual label. The representative label must be an accurate representation of the label that will be affixed to the dietary supplement distributed. We also agree that it would be acceptable to cross-reference the physical location of the actual or representative label.

Finally, because the actual or representative label is a record that you must make and keep in accordance with final § 111.610 in final subpart P, it must be readily available during the retention period for inspection or copying by FDA. Thus, we are revising proposed § 111.45(b)(6) (final § 111.210(g)) as discussed above.

(Comment 259) One comment states that a company that manufactures a dietary supplement under contract to another company would not have access to the product label.

(Response) Under final § 111.210(g) a company that manufactures a dietary supplement under contract could comply with the requirement by, for example, providing the name and address of the company who contracted for the manufacture of the batch as the cross-reference to the physical location of the label.

8. Final § 111.210(h)(1)

Final § 111.210(h)(1) requires that the master manufacturing record include written instructions for specifications for each point, step, or stage in the manufacturing process where control is necessary to ensure the quality of the dietary supplement and that the dietary supplement is packaged and labeled as specified in the master manufacturing record. Final § 111.210(h)(1) is similar to proposed § 111.45(b)(8)(i) which would require that the master manufacturing record include written instructions for specifications for each point, step, or stage in manufacturing the dietary supplement necessary to prevent adulteration. Final § 111.210(h)(1) includes changes that we are making for consistency with final § 111.70(a).

We did not receive comments specific to proposed § 111.45(b)(8)(i).

9. Final § 111.210(h)(2)

Final § 111.210(h)(2) requires that the master manufacturing record include written instructions for procedures for sampling, and a cross-reference to procedures for tests or examinations. Final § 111.210(h)(2) derives from proposed § 111.45(b)(8)(ii), which would require that the master manufacturing record include written instructions for sampling and testing.

(Comment 260) A few comments object to including certain written instructions for sampling and testing procedures in the master manufacturing record. One comment states that this documentation, such as laboratory testing procedures, would be a burdensome task and should be maintained separate from the master manufacturing record and be retrievable by appropriate cross-referencing information.

(Response) As we discussed in the preamble to the 2003 CGMP Proposal (68 FR 12157 at 12204), the written instructions are similar to a recipe. As such, the written instructions must include instructions related to procedures for sampling plans so you can collect appropriate samples for tests or examinations. We agree, however, that it is not necessary for the master manufacturing record to include written instructions for tests or examinations. Accordingly, we have revised the provision to permit the master manufacturing record to include a cross-reference to the procedures for tests or examinations. The final rule includes a requirement that you establish and follow written procedures for laboratory operations, including for tests and examinations that you conduct to determine whether specifications are met (final § 111.303). In essence, these written procedures for tests and examinations would constitute the written instructions that we proposed under § 111.45(b)(8)(ii) for testing procedures. This requirement for written procedures is generally described in section IV of this document.

10. Final § 111.210(h)(3)

Final § 111.210(h)(3) requires that the master manufacturing record include written instructions for specific actions necessary to perform and verify each point, step, or stage in the manufacturing process where control is necessary to ensure the quality of the dietary supplement and that the

dietary supplement is packaged and labeled as specified in the master manufacturing record. Final § 111.210(h)(3) derives from proposed § 111.45(b)(8)(iii) which would require that the master manufacturing record include written instructions for specific actions necessary to perform and verify each point, step, or stage necessary to meet specifications and otherwise prevent adulteration. Final § 111.210(h)(3) includes changes for consistency with final § 111.70(a).

Final § 111.210(h)(3)(i) requires that the specific actions include verifying the weight or measure of any component and verifying the addition of any component. Final § 111.210(h)(3)(ii) requires that, for manual operations, the specific actions include: (1) One person weighing or measuring a component and another person verifying the weight or measure and (2) one person adding a component and another person verifying the addition. Final § 111.210(h)(3)(i) and (h)(3)(ii) derive from proposed § 111.45(b)(8)(iii).

(Comment 261) Some comments suggest the requirement to have more than one person involved in performing and verifying each point, step, or stage in the manufacturing process is overly prescriptive and that alternative, reliable methods for verifying the weighing and addition of components should be permitted. One comment explains many manufacturers use bar code systems to identify the weight and identity of components both before and after weighing. In such cases, a computer generated weight record and corresponding bar code can be created and affixed to the container by one individual as reliable verification of the material's contents and weight. Likewise, the addition of components to a blender can be adequately controlled and verified by one person through scanning technology that allows reliable

verification of the identity and weight of components added to a blender without the need for a second person.

(Response) These comments describe a system partially under the control of automated equipment. Final § 111.30 establishes a series of requirements for automated equipment. We agree that, with such requirements in place for an automated system such as that described by the comments, the requirement to verify the weight or measure of a component, or to verify the addition of a component, can be achieved without requiring that one person do the weighing or measuring and another person verify the weighing or measuring and without requiring that one person add the component and another person verify the addition. Therefore, final § 111.210(h)(3) provides both that the written instructions must include verifying the weight or measure of any component and verifying the addition of any component and that, for manual operations, the written instructions must include: (1) One person weighing or measuring a component and another person verifying the weight or measure and (2) one person adding a component and another person verifying the addition. The final rule makes clear that there must be a verification step and gives firms flexibility, when the weighing or addition is not done manually, to determine how they would accomplish the verification.

11. Final § 111.210(h)(4)

Final § 111.210(h)(4) requires that the master manufacturing record include written instructions for special notations and precautions to be followed. Final § 111.210(h)(4) derives from proposed § 111.45(b)(8)(iv). We did not receive comments specific to proposed § 111.45(b)(8)(iv).

12. Final § 111.210(h)(5)

Final § 111.210(h)(5) requires that the master manufacturing record include written instructions for corrective action plans for use when a specification is not met. Final § 111.210(h)(5) derives from proposed § 111.45(b)(8)(v).

(Comment 262) Several comments argue pre-established corrective action plans are not useful for complex failure scenarios, and that the quality control unit should instead approve corrective action procedures on a case-by-case basis. One comment suggests the rule should refer to “procedures” rather than specifying “corrective action plans.”

(Response) We acknowledge that corrective action plans would be focused on each point, step, or stage where control is necessary to ensure the quality of the dietary supplement. We also acknowledge that it may not be practical to establish a corrective action plan for all foreseeable circumstances. In circumstances such as the complex failure scenario described by the comments, the documentation of the material review and disposition decision (rather than the corrective action plan) would identify the action taken to correct, and prevent a recurrence of, the deviation and discuss what you did with the batch (final § 111.140(b)(3)(iv) and (b)(3)(v)). However, we disagree that the fact that it may not be practical to establish a corrective action plan for all foreseeable circumstances means you could not establish a corrective action plan at each point, step, or stage where you can, in fact, predict a scenario and provide a plan for action when that scenario presents itself. Therefore, for any circumstance you can predict, final § 111.210(h)(5) requires that you establish corrective action plan.

F. Quality Control Responsibility (Proposed § 111.45(c))

In proposed § 111.45(c) we would require the quality control unit to review and approve each master manufacturing record and any modifications to a master manufacturing record. As part of the reorganization, this requirement is set forth under final § 111.123(a) in subpart F for quality control personnel. There is no reason to repeat the requirement in final subpart H and, thus, it does not appear in final subpart H.

XIV. Comments on the Production and Process Control System: Requirements for the Batch Production Record (Final Subpart I)

A. Organization of Final Subpart I

In the 2003 CGMP Proposal, the proposed requirements for the batch production record were set forth in § 111.50. As shown in table 10 of this document, we are setting forth the requirements for the batch production record in a distinct subpart (final Subpart I—Production and Process Control System: Requirements for the Batch Production Record) that contains the requirements that derive from proposed § 111.50. In addition, we are moving some proposed requirements from §§ 111.35 and 111.37 into final subpart I. Table 10 lists the sections in final subpart I and identifies the provisions that form the basis for the final rule.

TABLE 10.—DERIVATION OF SECTIONS IN FINAL SUBPART I

Final Rule	2003 CGMP Proposal
§ 111.255 What is the requirement to establish a batch production record?	§ 111.50(a), (b), and (i)
§ 111.260 What must the batch record include?	§ 111.35(i)(2), (j), (m), and (o)(2) § 111.37(b)(3), (b)(5), and (b)(9) § 111.50(c)(1) through (c)(11), (c)(13), (c)(14), (d)(2), (e), and (g) § 111.70(b)(6), (e), and (g)

The requirements in final subpart I are set forth from the perspective of the manufacture of a batch of a dietary supplement. However, you must comply with the requirement to prepare and follow a “batch production record” or a “batch record” regardless of whether you manufacture a batch or whether you package or label product you receive from a supplier for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier). As discussed in section VI of this document, if you are a packager or labeler, you only need to include those parts relevant to your process. For example, if you are a labeler under final § 111.260(e) you would not need to include the identity and weight or measure of each component used, because you would be starting from packages that already had been filled.

B. Highlights of Changes to the Proposed Requirements for the Batch Production Record

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.

- Does not use the term “shipment lot” when referring to components.

2. Changes Associated With the Reorganization

- Several provisions derive in whole or in part from proposed §§ 111.35, 111.37, or 111.70.

- Several requirements in proposed § 111.50 are redundant to requirements set forth in other subparts and are not repeated in subpart I.

- Several proposed requirements for reprocessing are moved to final § 111.90 in final subpart E.

- The proposed requirement to collect reserve samples of each batch of dietary supplement is moved to final § 111.83 in subpart E, where we clarify that the requirement relates to each lot of packaged and labeled dietary supplement rather than to a finished batch awaiting packaging and labeling.

3. Changes After Considering Comments

The final rule:

- Provides flexibility for firms to document information about the maintenance, cleaning, and sanitizing of equipment used in producing the batch in either the batch production record or in individual equipment logs that it cross-references in the batch production record.

- Provides flexibility for firms to include in the batch production record either the results of any testing or examination performed, or a cross-reference to the results of any testing or examination.

C. What Is the Requirement to Establish a Batch Production Record? (Final § 111.255)

Final § 111.255(a) requires you to prepare a batch production record every time you manufacture a batch of a dietary supplement. Final § 111.255(b) requires that the batch production record include complete information relating to the production and control of each batch. Final § 111.255(a) and (b) derive from proposed § 111.50(a), with a nonsubstantive revision that divides the proposed requirements into two separate paragraphs.

Final § 111.255(c) requires your batch production record to accurately follow the appropriate master manufacturing record and you to perform each

step in the production of the batch. Final § 111.255(c) derives from proposed § 111.50(b).

Final § 111.255(d) requires you to make and keep batch production records in accordance with subpart P. Final § 111.255(d) derives from proposed § 111.50(i) with editorial changes associated with the reorganization.

We did not receive comments specific to proposed § 111.50(a), (b), or (i).

D. What Must the Batch Record Include? (Final § 111.260)

1. Final § 111.260(a)

Final § 111.260(a) requires the batch production record to include the batch, lot, or control number: (1) Of the finished batch of dietary supplement and (2) that you assign in accordance with § 111.415(f) for each lot of packaged and labeled dietary supplement from the finished batch of dietary supplement, and for each lot of dietary supplement, from the finished batch of dietary supplement, that you distribute to another person for packaging or labeling.

Final § 111.260(a) derives, in part, from proposed § 111.50(c)(1), which would require the batch, lot, or control number in the batch production record. Consistent with comments that requested that we clarify responsibilities when more than one party is involved with the manufacturing, packaging, labeling, or holding of a dietary supplement (see section VI of this document), we have added the requirements of final § 111.260(a)(1), (a)(2)(i), and (a)(2)(ii) to ensure that you are able to determine the manufacturing history and control of the packaged and labeled dietary supplement from all stages of manufacturing through distribution, and to be consistent with other provisions of this final rule. In the discussion of subpart L (section XVII of this document), we explain in detail final § 111.410(d), which requires you to be able to determine the complete manufacturing history and control of the packaged and labeled

dietary supplement through distribution. In that same section, we explain final § 111.415(f) which requires you to assign a batch, lot, or control number to each lot of packaged and labeled dietary supplement from a finished batch and each lot of dietary supplement from a finished batch that you distribute to another person for packaging and labeling. In that way, these batch, lot, or control numbers can be used to determine the manufacturing history and control of the batch. However, you can determine how you track the batch, lot, or control number of the packaged and labeled dietary supplement, or dietary supplement you send to another person for packaging and labeling, to a distributed dietary supplement.

We did not receive comments specific to proposed § 111.50(c)(1). We respond to comments relevant to final subpart L in section XVII of this document.

2. Final § 111.260(b)

Final § 111.260(b) requires that the batch production record include the identity of equipment and processing lines used in producing the batch and derives from proposed § 111.50(c)(3).

We did not receive comments specific to proposed § 111.50(c)(3).

3. Final § 111.260(c)

Final § 111.260(c) requires that the batch production record include the date and time of the maintenance, cleaning, and sanitizing of the equipment and processing lines used in producing the batch, or a cross-reference to records, such as individual equipment logs, where this information is retained. Final § 111.260(c) derives from proposed § 111.50(c)(4).

(Comment 263) Many comments argue that it is not necessary or appropriate to retain the records of maintenance, cleaning, and sanitizing

equipment and processing lines in the batch production record. These comments request that the final rule provide flexibility to retain such records in individual equipment files or log books for easy access. One comment recommends the requirement to retain such records be set forth within subpart D.

(Response) As discussed in section IX of this document (final § 111.35(b)(2)), we agree with these comments. Consistent with final § 111.35(b)(2), final § 111.260(c) provides flexibility to retain the records of maintenance, cleaning, and sanitizing equipment and processing lines in either the batch production record or another record you cross-reference in the batch production record.

4. Final § 111.260(d)

Final § 111.260(d) requires that the batch production record include the unique identifier you assigned to each component (or, when applicable, to a product you receive from a supplier for packaging or labeling as a dietary supplement), packaging, and label used. Final § 111.260(d) derives from proposed § 111.50(c)(5), which would require that the batch record include the shipment lot unique identifier of each component, dietary supplement, packaging, and label used. Consistent with the convention we are establishing under final §§ 111.80(a), 111.155, and 111.160, final § 111.260(d) does not use the term “shipment lot.”

We did not receive comments specific to proposed § 111.50(c)(5).

5. Final § 111.260(e) and (f)

Final § 111.260(e) requires that the batch production record include the identity and weight or measure of each component used and derives from proposed § 111.50(c)(6).

Final § 111.260(f) requires that the batch record include a statement of the actual yield and a statement of the percentage of theoretical yield at appropriate phases of processing. Final § 111.260(f) derives from proposed § 111.50(c)(9).

(Comment 264) A few comments argue that the requirements in proposed § 111.50(c)(6) are not applicable to continuous operations and that yield information required in proposed § 111.50(c)(9) is irrelevant for quality control in continuous operations used for producing dietary ingredients. One of these comments also discusses “continuous operations,” such as a continuous operation built adjacent to a soy crushing or vegetable oil refinery to receive a continuous side stream flow from that operation (see the discussion of final § 111.155(c) in section XII of this document). This comment explains that in such operations, quarantine and quality control approval occurs after the material has been isolated and concentrated in a stable matrix suitable for holding.

(Response) Based on the limited information provided by these comments, it appears that they are describing the manufacture of a “dietary ingredient” or other component that will subsequently be used in the manufacture of a dietary supplement. Therefore, in this scenario, the identity and weight or measure of the stable matrix must be taken. The statement of the actual yield and the theoretical yield refers to the batch in which the stable matrix is added as a component.

6. Final § 111.260(g)

Final § 111.260(g) requires that the batch production record include the actual results obtained during any monitoring operation. Final § 111.260(g) derives from proposed § 111.35(o)(2) which would require you to make and

retain records of the actual results obtained during monitoring of the in-process production. Consistent with the reorganization we are specifying that the records of monitoring be located in the batch production record, because the monitoring is associated with the batch production.

We did not receive comments specific to proposed § 111.35(o)(2).

7. Final § 111.260(h)

Final § 111.260(h) requires that the batch production record include the results of any testing or examination performed during the batch production, or a cross-reference to such results. Final § 111.260(h) derives from proposed § 111.50(c)(10) which would require you to record the actual results of any testing performed during production of the batch.

(Comment 265) A few comments object to the requirement in proposed § 111.50(c)(10) that actual test results be included in the batch production record. These comments state test results are typically retained in other records, such as laboratory records, and that it would be duplicative to include such results in the batch production record. One comment states the “actual” (original record of) test results may not be available to the manufacturer when the testing is performed electronically or an outside laboratory does the testing. This comment adds for test results obtained in-house, original records are typically kept as part of the master laboratory records and cross-referenced in batch records.

(Response) After considering these comments, we are providing flexibility to either include the results of tests or examinations in the batch production record, or provide a cross-reference to such results. We note that final § 111.260(h) does not require that you have the original documentation of the test results. If an outside laboratory has performed testing for you, you must

obtain a copy of the test results and include these in your batch production record or in another appropriate record that you can cross-reference and make readily available for inspection.

8. Final § 111.260(i)

Final § 111.260(i) requires that the batch production record include documentation that the finished dietary supplement meets specifications established in accordance with § 111.70(e) and (g). Final § 111.260(i) derives from proposed § 111.50(c)(11). We have made a change to identify which required specifications the dietary supplement must meet.

We did not receive comments specific to proposed § 111.50(c)(11).

9. Final § 111.260(j)

Final § 111.260(j) sets forth the requirements for documentation you must make and include in the batch production record, at the time of performance, of the manufacture of the batch. Final § 111.260(j) derives from proposed § 111.50(c)(2) and (c)(7).

a. *Final §111.260(j)(1)*. Final § 111.260(j)(1) requires documentation, at the time of performance, of the date on which each step of the master manufacturing record was performed. Final §111.260(j)(1) derives from proposed § 111.50(c)(2). We did not receive comments specific to proposed § 111.50(c)(2).

b. *Final §111.260(j)(2)*. Final § 111.260(j)(2) requires documentation, at the time of performance, of the initials of the persons performing each step in the master manufacturing record. Final § 111.260(j)(2) derives from the second part of proposed § 111.50(c)(2),(c)(7) and (c)(8).

(Comment 266) One comment asks whether the persons responsible for batch production must be identified by name or by position.

(Response) The requirement is for the initials of the name of the person rather than for identification of the position. Requiring that the record include the initials of the person(s) performing each step in the master manufacturing record means that the person performing the step is the person who physically initials the batch record at the time the person performs the step. The intent is for the person to acknowledge that he or she performed the requirement rather than to merely provide information that would identify that person.

(Comment 267) One comment asks whether we will allow electronic signatures for batch production records, laboratory test results, and quality control unit documentation. The comment notes that many companies have fully computerized, automated production and quality control management systems that utilize password-protected (or otherwise secure) means of entering data at key quality control steps.

(Response) The use of electronic signatures is governed by our regulations in part 11, which control whether electronic signatures are permitted. Our guidance entitled "Guidance for Industry Part 11, Electronic Records; Electronic Signatures—Scope and Application," available at <http://www.fda.gov/cder/guidance/5667fnl.htm>, discusses the use of electronic signatures (Ref. 33).

c. *Final § 111.260(j)(2)(i) through § 111.260(j)(2)(iv)*. Final § 111.260(j)(2)(i) requires you to document at the time of performance the initials of the person responsible for weighing or measuring each component used in the batch, and final § 111.260(j)(2)(ii) requires you to document at the time of performance the initials of the person responsible for verifying the weight or measure of each component used in the batch. Final § 111.260(j)(2)(i) and (j)(2)(ii) derive from proposed § 111.50(c)(2)(i) and (c)(7), respectively.

Final § 111.260(j)(2)(iii) requires you to document, at the time of performance, the initials of the person responsible for adding the component to the batch; and final § 111.260(j)(2)(iv) requires you to document, at the time of performance, the initials of the person responsible for verifying the addition of components to the batch. Final § 111.260(j)(2)(iii) derives from proposed § 111.50(c)(2)(ii) and final § 111.260(j)(2)(iv) derives from proposed § 111.50(c)(8).

We did not receive comments specific to proposed § 111.50(c)(2)(i) and (c)(2)(ii) or § 111.50(c)(7) and (c)(8).

10. Final § 111.260(k)

Final § 111.260(k) sets forth the requirements for documentation you must make and include in the batch production record, at the time of performance, of the packaging and labeling operations. Final § 111.260(k) derives from proposed § 111.70(g) which we discuss in the following paragraphs.

In final § 111.260(k)(3), we are eliminating proposed § 111.70(g)(4) which would require that the documentation include any material reviews and disposition decisions for packaging and labels, because it would be redundant to final § 111.180(b)(4)(ii)(D).

a. *General comments on proposed § 111.70(g).*

(Comment 268) Some comments assert that the requirement of proposed § 111.70(g) that all packaging releases be placed in the batch production record is unnecessary. According to the comments, most packaging material lots are used in multiple batches. The comments assert that a requirement for this disposition information to be copied into each batch production record is unnecessary as long as lot traceability exists and this information is kept in a central file.

(Response) These comments may have misinterpreted proposed § 111.70(g). It would require that the documentation in the batch production record for packaging and label operations include: (1) The identity and quantity of the packaging and labels used and reconciliation of any discrepancies between issuance and use, (2) the examination conducted in accordance with proposed § 111.70(b)(7), (3) the conclusions reached from retests conducted in accordance with proposed § 111.70(e), and (4) any material reviews and disposition decisions for packaging and labels. None of these proposed requirements would require that “packaging releases” be included in the batch record.

The requirements for documentation for packaging you receive are set forth in final § 111.180(b) in subpart G.

b. *Final § 111.260(k)(1)*. Final § 111.260(k)(1) requires the documentation of packaging and labeling operations to include the unique identifier you assigned to packaging and labels used, the quantity of the packaging and labels used, and, when label reconciliation is required, reconciliation of any discrepancies between issuance and use of labels. Final § 111.260(k)(1) derives from proposed § 111.70(g)(1) which would require that the documentation include the identity and quantity of the packaging and labels used and reconciliation of any discrepancies between issuance and use. For consistency with other provisions of this final rule, such as final § 111.160(e)(1), final § 111.260(k)(1) requires “the unique identifier you assigned to packaging and labels used,” rather than “the identity of packaging and labels used.” Final § 111.260(k)(1) also includes changes we are making after considering comments.

(Comment 269) Some comments assert comprehensive label reconciliation should not be required if appropriate electronic controls are instituted to ensure that correct labels are used during labeling operations. The comments state this alternative is permitted for labeling operations for drug products, which are generally identical or similar in nature to labeling operations for dietary supplements. As such, the comments assert the same flexibility should be afforded to dietary supplement manufacturers. Some comments specifically suggest changing the language of proposed § 111.70(g)(1) to read “The identity and quantity of the packaging and labels used and either reconciliation of any discrepancies between issuance and use or use of appropriate electronic or electromechanical equipment to conduct a 100-percent examination for labeling during or after completion of finishing operations.”

(Response) We agree that label reconciliation need not be required for cut or rolled labels if a 100-percent examination for correct labels is performed by appropriate electronic or electromechanical equipment during or after completion of finishing operations. Thus we have made two changes in this final rule in addition to the changes in final § 111.260(k)(1) that provide there must be label reconciliation when such reconciliation is required either to account for discrepancies or to ensure the use of the label that is specified in the master manufacturing record. First, we have revised the final rule in subpart L (for packaging and labeling operations) to provide that you need not conduct label reconciliation if a 100-percent examination for correct labels is performed by appropriate electronic or electromechanical equipment during or after completion of finishing operations (see discussion of final § 111.410(b) in subpart L in section XVI of this document). Second, final § 111.260(k)(1), requires you to include documentation in the batch production of

reconciliation of any discrepancies between issuance and use of labels only when label reconciliation is required.

c. *Final § 111.260(k)(2)*. Final § 111.260(k)(2) requires the documentation of packaging and labeling operations to include an actual or representative label, or a cross-reference to the physical location of the actual or representative label specified in the master manufacturing record. Final § 111.260(k)(2) derives from proposed § 111.50(c)(12) which would require that the batch production record include copies of all container labels used and the results of examinations conducted during the label operation to ensure that the containers have the correct label.

(Comment 270) A few comments ask that we clarify the container labels that proposed § 111.50(c)(12) is referring to. Specifically, these comments ask whether proposed § 111.50(c)(12) is referring to finished product labels, bulk material labels, or in-process container labels. One comment asserts proposed § 111.50(c)(12) is unnecessary for ensuring the dosage form of dietary supplements meets specifications.

One comment finds proposed § 111.50(c)(12) confusing, because it does not specify what is meant by “label operation.” This comment notes that during the course of manufacturing operations, containers holding in-process materials are often labeled but the comment assumes that proposed § 111.50(c)(12) does not require the retention of copies of in-process container labels, which would not add significant value toward the assurance of a quality product.

In general, these comments ask for clarification of proposed § 111.50(c)(12), and suggest it be deleted.

(Response) Proposed § 111.50(c)(12) referred to the product label that would be affixed to the containers that hold the packaged and labeled dietary supplement. We did not receive any comments that a related requirement (in proposed § 111.45(b)(7) in the master manufacturing record) was confusing or needed clarification. We therefore believe that the requirement that the batch production record include a label will be clearer if we state the requirement in a way that is similar to the requirement in proposed § 111.45(b)(7). However, because comments to proposed § 111.45(b)(7) persuaded us to provide flexibility for (1) having a representative label rather than an actual label and (2) cross-referencing the physical location of the actual or representative label that is specified in the master manufacturing record, we are providing the same flexibility for having a label in the batch production record. Therefore, we are revising the proposed requirement that the batch production record include “copies of all container labels used” so that, under final § 111.260(k)(2), the batch production record must include an actual or representative label, or a cross-reference to the physical location for the actual or representative label that is specified in the master manufacturing record.

However, we are not requiring in final § 111.260(k)(2) that the batch production record include the results of examinations conducted during the label operation to ensure that the containers have the correct label that is specified in the master manufacturing record, because this would be redundant to final § 111.260(k)(3).

d. *Final § 111.260(k)(3)*. Final § 111.260(k)(3) requires that the documentation of packaging and labeling operations include the results of any tests or examinations conducted on packaged and labeled dietary supplements (including repackaged or relabeled dietary supplements), or a cross-reference

to such results. Final § 111.260(k)(3) combines the proposed requirements of proposed § 111.70(g)(2) which would require that the documentation include the results of examinations conducted in accordance with proposed § 111.70(b)(7), and proposed § 111.70(g)(3) which would require that the documentation include the conclusions from retests conducted in accordance with proposed § 111.70. For consistency with other requirements for documentation that must be in the batch record, final § 111.260(k)(3) requires you to include “the results of any tests or examinations,” rather than “the examination” (proposed § 111.70(g)(2)) and “conclusions” (proposed § 111.70(g)(3)). Final § 111.260(k)(3) also includes editorial revisions associated with combining proposed § 111.70(g)(2) and (g)(3).

We did not receive comments specific to proposed § 111.70(g)(2) or (g)(3).

11. Final § 111.260(l)

Final § 111.260(l) sets forth the requirements for documentation quality control personnel must make at the time of performance and that must be included in the batch production record. Final § 111.260(l) derives from proposed §§ 111.35(i)(2), (j), (m), (o)(2); 111.37(b)(3), (b)(5), and (b)(9); 111.50(c)(1) through (c)(11), (c)(13), (c)(14), (d)(2), (e), and (g); 111.70(b)(6); and 111.70(g).

a. *Final § 111.260(l)(1)*. Final § 111.260(l)(1) requires quality control personnel to document at the time of performance the review of the batch production record. Final § 111.260(l)(1) derives from the following proposed regulations:

- § 111.50(d), which would require that the quality control unit review in accordance with § 111.37(b)(5) the batch production record established in § 111.50(c); and

- § 111.50(e), which would require that the quality control unit document at the time of performance in accordance with § 111.37(c), the review performed in accordance with § 111.50(d).

Final § 111.260(l)(1) includes editorial changes associated with the reorganization. We did not receive comments specific to proposed § 111.50(d) or (e).

b. *Final § 111.260(l)(1)(i)*. Final § 111.260(l)(1)(i) requires the documentation by quality control personnel to include review of any monitoring operation required under subpart E. Final § 111.260(l)(1)(i) derives from proposed § 111.35(i)(2) which would require that you review, among other things, the results of the monitoring of the in-process control points, steps, or stages to ensure specifications are met. As discussed in section XI of this document (final § 111.123(a)(3)), the final rule requires quality control personnel to review the required monitoring.

We did not receive comments specific to proposed § 111.35(i)(2).

c. *Final § 111.260(l)(1)(ii)*. Final § 111.260(l)(1)(ii) requires the documentation by quality control personnel to include the review by quality control personnel of the results of any tests or examinations, including tests or examinations conducted on components, in-process materials, finished batches of dietary supplements, and packaged and labeled dietary supplements. Final § 111.260(l)(1)(ii) derives from the following proposed provisions:

- Proposed § 111.50(e)(1) which would require that the documentation by the quality control unit include review of component, dietary ingredient, and dietary supplement receiving records, including review of testing and examination results and

- Proposed § 111.37(b)(9) which would require, in part, the quality control unit to review all testing results.

(Comment 271) A few comments assert that the proposed requirement that the quality control unit review receiving records as part of its review of the batch record is redundant and should be eliminated. One comment argues that it is unnecessarily burdensome to require the quality control unit to re-review and cross-reference all receiving records, noting that the quality control unit already has performed a review of these records when the components or dietary supplements were received, approved, and released for use. The comment asserts the quality control unit should only have to repeat this review if it is conducting an investigation or a material review.

(Response) We agree with the comments. Therefore, final § 111.260(l)(1)(ii) retains the requirements of proposed §§ 111.37(b)(9) and 111.50(e)(1) to review the results of testing and examination, but does not require quality control personnel to document, as part of the review of the batch record, receiving records for components and dietary supplements.

d. *Final § 111.260(l)(2)*. Final § 111.260(l)(2) requires that the documentation by quality control personnel include that quality control personnel approved or rejected any reprocessing or repackaging. Final § 111.260(l)(2) derives from proposed § 111.50(c)(14) which would require that the batch production record include the signature of the quality control unit to document its review of the batch production record and any approval for reprocessing or repackaging. For consistency with other provisions in this final rule (such as final § 111.90), final § 111.260(l)(2) includes a revision that quality control personnel must clearly choose between approving—or rejecting—any reprocessing or repackaging.

We did not receive comments specific to proposed § 111.50(c)(14).

e. *Final § 111.260(l)(3)*. Final § 111.260(l)(3) requires the documentation by quality control personnel to include that it approved and released, or rejected, the batch for distribution, including any reprocessed batch. Final § 111.260(l)(3) derives from the following proposed regulations:

- Proposed § 111.37(b)(5) which would require, in part, the quality control unit to review the batch production record to approve the batch for release for distribution;
- Proposed § 111.50(d)(2) which would require the quality control unit not to approve and release for distribution any batch of dietary ingredients or dietary supplement that does not meet all specifications; and
- Proposed § 111.50(g) which would require, in part, the results of the reevaluation by the quality control unit to be documented in the batch production record.

For consistency with other provisions of this final rule (such as final § 111.90), final § 111.260(l)(3) requires that quality control personnel must clearly choose between approving—or rejecting—the batch for distribution. We did not receive comments specific to those parts of proposed §§ 111.37(b)(5) or 111.50(d)(2) that we are setting forth in final § 111.260(l)(3).

f. *Final § 111.260(l)(4)*. Final § 111.260(l)(4) requires the batch production record to include documentation, at the time of performance, that quality control personnel approved and released, or rejected, the packaged and labeled dietary supplement, including any repackaged or relabeled dietary supplement. Final § 111.260(l)(4) derives from the following proposed regulations:

- Proposed § 111.37(b)(3) which would require, in part, that the quality control unit approve or reject all dietary supplements and

- Proposed § 111.70(e) which would require, in part, that any repackaged or relabeled dietary supplement meet all specifications and that the quality control unit must approve or reject their release for distribution.

We did not receive comments specific to those parts of proposed §§ 111.37(b)(3) or 111.70(e) that we are setting forth in final § 111.260(l)(4).

12. Final § 111.260(m)

Final § 111.260(m) requires the batch production record to include documentation, at the time of performance, of any required material review and disposition decision. Final § 111.260(m) derives from the following proposed provisions:

- Proposed § 111.50(c)(13) which would require that the batch production record include any documented review and disposition decision and
- Proposed § 111.35(j) which would require that the person who conducts the material review and makes the disposition decision document that activity, at the time of performance, in the batch production record.

We did not receive comments specific to proposed §§ 111.35(j) or 111.50(c)(13).

13. Final § 111.260(n)

Final § 111.260(n) requires that the batch production record include documentation, at the time of performance, of any reprocessing. We have added this requirement in conjunction with the requirement for written procedures for the quality control operations for approving or rejecting any reprocessing, discussed generally in section IV of this document.

E. Review of Batch Production Record Deviations (Proposed § 111.50(d)(1), (e)(2), (e)(3), and (e)(4))

Proposed § 111.50(d)(1) would require, if a batch deviates from the master manufacturing record, including any deviation from specifications, the quality control unit to conduct a material review and make a disposition decision and record any decision in the batch production record. Under final § 111.87 quality control personnel must conduct any required material review and make any required disposition decision; under final § 111.113(a)(2) quality control personnel must conduct a material review and make a disposition decision if a batch deviates from the master manufacturing record, including any deviation from specifications. Given the requirements of final §§ 111.87 and 111.113, it would be redundant to include proposed § 111.50(d)(1) in final subpart I.

Proposed § 111.50(e)(2) would require that the review of the batch production record and documentation by the quality control unit include identification of any deviation from the master manufacturing record that may have caused a batch or any of its components to fail to meet specifications identified in the master production record. Proposed § 111.50(e)(3) would require that the review of the batch production record and documentation by the quality control unit include records of investigations, conclusions, and corrective actions performed in accordance with proposed § 111.50(d). Proposed § 111.50(e)(4) would require that the review of the batch production record and documentation by the quality control unit include the identity of the person qualified by training and experience who performed the investigation in accordance with § 111.50(d).

Each of these requirements is already included in final § 111.140(b)(3) which sets forth the requirements for the documentation that quality control personnel must include for any required material review and disposition decision. In addition, under final § 111.260(m), the batch production record must include documentation of any required material review and disposition decision. Given the requirements of final §§ 111.140(b)(3) and 111.260(m), it would be redundant to include proposed § 111.50(e)(2), (e)(3), and (e)(4) in final subpart I, and we are not including them.

XV. Comments on Production and Process Control System: Requirements for Laboratory Operations (Final Subpart J)

A. Organization of Final Subpart J

In the 2003 CGMP Proposal, the proposed requirements for production and process controls for laboratory operations were set forth in proposed § 111.60(a) through (d). As shown in table 11 of this document, we are reorganizing the requirements for laboratory operations into a distinct subpart (final Subpart J—Production and Process Control System: Requirements for Laboratory Operations). Table 11 lists the sections in final subpart J and identifies the proposed sections that form the basis of the final rule.

TABLE 11.—DERIVATION OF SECTIONS IN FINAL SUBPART J

Final Rule	2003 CGMP Proposal
§ 111.303 What are the requirements under this subpart J for written procedures?	N/A
§ 111.310 What are the requirements for the laboratory facilities that you use?	§ 111.60(a)
§ 111.315 What are the requirements for laboratory control processes?	§ 111.60(b)(1)
§ 111.320 What requirements apply to laboratory methods for testing and examination?	§ 111.60(c) and (d)

TABLE 11.—DERIVATION OF SECTIONS IN
FINAL SUBPART J—Continued

Final Rule	2003 CGMP Proposal
§ 111.325 Under this subpart J, what records must you make and keep?	§ 111.60(b)(2) and (b)(3)

B. Highlights of the Changes to the Proposed Requirements for Laboratory Operations

1. Revisions

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

This subpart contains fewer details, compared to the 2003 CGMP Proposal, regarding the requirements for collecting representative samples and for testing, because these details are set forth elsewhere in this final rule (i.e., in final §§ 111.75 and 111.80) and would be redundant in final subpart J.

3. Changes After Considering Comments

The final rule:

- Includes a new requirement to establish and follow written procedures for laboratory operations, including written procedures for the tests and examinations you conduct to determine whether or not specifications are met.
- Requires you to identify and use the appropriate “scientifically valid method,” rather than an appropriate “validated testing method,” for each established specification for which testing or examination is required to determine whether the specification is met.

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

(Final § 111.303)

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 § 111.303 requires you to establish and follow written procedures for laboratory operations, including written procedures for the tests and examinations you conduct to determine whether specifications are met.

D. What Are the Requirements for the Laboratory Facilities That You Use?

(Final § 111.310)

Final § 111.310 requires you to use adequate laboratory facilities to perform whatever testing and examinations are necessary to determine whether: (1) Components that you use meet specifications; (2) in-process specifications are met as specified in the master manufacturing record; and (3) dietary supplements that you manufacture meet specifications. Final § 111.310(a) is substantially similar to proposed § 111.60(a). The requirement for “adequate laboratory facilities” is to ensure that the facilities used are designed and suitable for carrying out the necessary tests and examinations. Other CGMP requirements of this final rule would apply to the manufacturer’s laboratory facilities, such as Subpart C—Physical Plant and Grounds, and Subpart D—Equipment and Utensils, and should be considered in assessing the adequacy of the laboratory facilities. If the tests and examinations are carried out by an outside laboratory, you will be responsible for ensuring that the test and examinations are adequately performed.

(Comment 272) One comment states that proposed § 111.60(a) would be highly disruptive to the dietary supplement industry and would impose a great burden on companies that traditionally rely on certification of ingredient suppliers. Some comments assert it would be redundant to require testing by companies who are suppliers of dietary ingredients, as well as by companies who receive the dietary supplements, to determine whether the dietary ingredients meet specifications.

(Response) The final rule already includes changes that address the concerns raised by these comments. As discussed in section X of this document regarding final § 111.75(a), the final rule permits the use of certificates of analysis for specifications other than the identity of a dietary ingredient.

E. What Are the Requirements for Laboratory Control Processes? (Final § 111.315)

Final § 111.315 sets forth the minimum laboratory control processes that you must establish and follow. These laboratory control processes must be reviewed and approved by quality control personnel.

1. Final § 111.315(a)

Final § 111.315(a) requires the laboratory control processes you establish and follow to include the use of criteria for establishing appropriate specifications. Final § 111.315(a) is identical to proposed § 111.60(b)(1)(ii).

We did not receive comments specific to proposed § 111.60(b)(1)(ii).

2. Final § 111.315(b)

Final § 111.315(b) requires you to establish and follow laboratory control processes that are reviewed and approved by quality control personnel,

including the use of sampling plans for obtaining representative samples, in accordance with subpart E, of: (1) Components, packaging, and labels; (2) in-process materials; (3) finished batches of dietary supplements; (4) product you receive for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier); and (5) packaged and labeled dietary supplements. Final § 111.315(b) derives from proposed § 111.60(b)(1)(iii)(A) through (b)(1)(iii)(E).

Final § 111.315(b) combines the proposed requirements of § 111.60(b)(1)(iii)(A) and (b)(1)(iii)(D) for consistency with final § 111.80(a) which combines the requirements to collect representative samples of components, packaging, and labels. However, for consistency with other requirements established by this final rule, we are separating the requirements to collect representative samples of “dietary supplements received” (which the final rule refers to as “product that you receive for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier,” or “received product”)) from the requirements to collect representative samples of components.

(Comment 273) Some comments note that proposed § 111.60(b)(1)(iii) restates the requirements, already contained in proposed § 111.37(b)(11)(i) through (b)(11)(iv), that the quality control unit collect representative samples. These comments request proposed § 111.60(b)(1)(iii) be deleted, because it is more appropriately described as a quality control function rather than as a laboratory function.

(Response) We disagree that the proposed requirement to use a sampling plan is more appropriately described as a quality control function than as a laboratory function. Under both the proposed and the final rule, the sampling

plans that are part of the laboratory control operations are subject to approval by quality control personnel (“unit” in the proposed rule) but are not developed by quality control personnel. We are making no changes based on this comment.

(Comment 274) One comment asserts sampling can be better accomplished at the point of packaging rather than at a laboratory remote from the packaging operation.

(Response) This comment misinterprets proposed § 111.60(b)(1)(iii) which proposed to establish a process (i.e., the use of a sampling plan) rather than to direct that a particular operating unit (such as a laboratory) collect samples. We are making no changes based on this comment.

3. Final § 111.315(c)

Final § 111.315(c) requires the laboratory control processes you establish and follow include use of criteria for selecting appropriate examination and testing methods. Final § 111.315(c) is identical to proposed § 111.60(b)(1)(i).

(Comment 275) One comment recommends that a contract laboratory hired by a person who is subject to the final rule be able to determine the specific type of test that is most appropriate.

(Response) Nothing in the final rule would preclude you from relying on the recommendation of the contract laboratory in selecting an appropriate test or examination. However, the manufacturer of the dietary supplement has the responsibility to comply with these CGMP requirements, including the requirement to select appropriate tests, regardless of who conducts the tests.

4. Final § 111.315(d)

Final § 111.315(d) requires the laboratory control processes you establish and follow to include use of criteria for selecting standard reference materials

used in performing tests and examinations. Final § 111.315(d) derives from proposed § 111.60(b)(1)(iv).

(Comment 276) Several comments support the use of standard reference materials. Some comments distinguish between a reference standard (which they describe as a highly purified compound that is well characterized and is used in quantitative assays for single chemical entities) and a reference material (which they describe as similar to a reference standard but with less specificity). These comments urge us to recognize the difference between reference standards and reference materials and to require the use of both in the final rule.

(Response) The comments that request we recognize a difference between certain types of reference materials are consistent with proposed § 111.60(b)(1)(iv) and with statements that we made in the preamble to the 2003 CGMP Proposal. We distinguished two general types of reference materials: (1) Compendia reference standards that do not require characterization and (2) noncompendia standards that should be of the highest purity that can be obtained by reasonable effort and that should be thoroughly characterized to ensure their identity, purity, quality, and strength. We recommended you use compendia reference standards whenever possible, and that you establish appropriately characterized in-house materials prepared from representative lots if no compendia reference standard exists.

We also discussed reference materials from the perspective of the type of test or examination. For organoleptic examinations, we described an authenticated plant reference material as material that has been authenticated as the correct plant species and correct plant part(s) by a qualified plant taxonomist. For microscopic and chemical tests (including calibration tests),

we described a reference material as a highly purified compound that is well characterized.

To the extent that the comments are recommending that both compendia reference standards and noncompendia reference standards comply with any final rule, this final rule would allow for the use of both compendia reference standards and noncompendia reference standards. However, to the extent that the comments are requesting this final rule require that both types of reference materials be used, we disagree. We see no reason to require, for example, that a firm with access to compendia standards be required to develop noncompendia standards. Likewise, given that we have acknowledged that noncompendia standards may be used, we see no reason to require the use of compendia standards in all circumstances.

(Comment 277) One comment expresses confusion about the preamble discussion of proposed § 111.60(b)(1)(iv) and suggests the preamble specify that reference standards be established appropriate to the assay procedure for which they are used.

(Response) Reference materials should be appropriate to the assay procedure for which they are used.

(Comment 278) Several comments recommend we acknowledge certain reference materials as authoritative sources for botanical ingredients, such as American Herbal Pharmacopoeia, European Pharmacopoeia, and the World Health Organization, in part because other sources include only a limited number of botanicals as supplements. In the comments' view, explicit acknowledgment by FDA would encourage manufacturers to use independent standards, increase CGMP compliance, and show that validation is not limited to quantitative chemical methods.

(Response) We decline to acknowledge certain reference materials as authoritative sources for botanical ingredients. Such a request is outside the scope of this final rule.

(Comment 279) One comment believes we should designate USP to develop appropriate standards.

(Response) This comment is outside the scope of this final rule.

5. Final § 111.315(e)

Final § 111.315(e) requires that the laboratory control processes you must establish and follow include use of test methods and examinations in accordance with established criteria. Final § 111.315(e) derives from proposed § 111.60(b)(1)(vi).

We did not receive comments specific to proposed § 111.60(b)(1)(vi).

F. What Requirements Apply to Laboratory Methods for Testing and Examination? (Final § 111.320)

1. Final § 111.320(a)

Final § 111.320(a) requires you to verify that laboratory examination and testing methodologies are appropriate for their intended use. Final § 111.320(a) is identical to proposed § 111.60(c).

(Comment 280) One comment states that this decision should be made by a qualified person, whether in-house or at a contract laboratory.

(Response) We agree. Nothing in the final rule would preclude you from relying on the judgment of a qualified person at a contract laboratory to satisfy the requirements of final § 111.320(a). We would not consider that a recommendation from a contract laboratory is any different from a recommendation from an operating unit of the manufacturer. However, the

manufacturer of the dietary supplement has the responsibility to comply with these CGMP requirements, including the requirement to select appropriate tests, regardless of who conducts the tests.

(Comment 281) One comment suggests modifying proposed § 111.60(c) to add “reference materials and/or reference standards” to the list of elements that must be verified to be appropriate for their intended use.

(Response) If reference materials and reference standards are used as part of the test or examination method, then such materials and standards are already required to be verified under the language in proposed § 111.60(c). Thus, there is no need for the modification and we decline to modify the language of final § 111.320(a).

2. Final § 111.320(b)

Final § 111.320(b) requires you to identify and use the appropriate scientifically valid method for each established specification for which testing or examination is required to determine whether the specification is met. Final § 111.320(b) derives from proposed § 111.60(d) which would require you to identify and use an appropriate validated testing method for each established specification for which testing is required to determine whether the specification is met. Final § 111.320(b) includes a provision associated with final § 111.75(h) which provides flexibility to use examinations as well as tests to determine whether specifications are met.

(Comment 282) Many comments express concern about the amount of testing required for the validation of the appropriate test method. Several comments object to the use of the terms “validations” and “validated” which they assert have a specific meaning in a pharmaceutical context and would be overly burdensome in this rule. Other comments assert that methods already

recognized as official standards do not need to be “validated,” but simply “verified” as to suitability. Some comments suggest substituting “scientifically valid testing method” for “appropriate validated testing method.” One comment suggests “qualifications” replace “validations.” Another comment suggests test methods need not be validated if they are “proven to be suitable under actual conditions of use.” Another comment suggests adding “established by the manufacturer” after “appropriate validated test method.”

One comment recommends the final rule give companies the flexibility to adopt the method most suitable to the ingredient they are testing, regardless of whether the method is, or is not, an “official method” such as those established by AOAC International or FDA.

(Response) In the preamble to the 2003 CGMP Proposal (68 FR 12157 at 12208), we stated that test method validation determines whether a newly-developed or existing test method is accurate, precise, and specific for its intended purpose and involves evaluating the test method on multiple occasions or in multiple test facilities. We explained that official methods, such as AOAC International methods, are validated in collaborative studies using several laboratories under identical conditions and that the AOAC International methods are often cited as “official validated methods.” We also explained that other method validations are conducted in a single laboratory by repeating the same test multiple times. Typical validation characteristics include accuracy, precision, specificity, detection limit, quantitation limit, linearity, range, and robustness.

The process of method validation discussed above is a formal process for demonstrating that procedures are suitable for their intended use. Although all methods that are formally validated are considered “scientifically valid,”

other methods that are based on scientific data or results published in, for example, scientific journals, references, text books, or proprietary research can be scientifically valid even if they are not formally “validated” in collaborative studies (68 FR 12157 at 12198).

We agree that companies should have flexibility to adopt the method most suitable to the ingredient they are testing. Consistent with the view that we expressed in the preamble to 2003 CGMP Proposal (68 FR 12157 at 12198), we believe that a scientifically valid method is one that is accurate, precise, and specific for its intended purpose. In other words, a scientifically valid method is one that consistently does what it is intended to do.

Because we acknowledge that methods that are based on scientific data or results published in, for example, scientific journals, references, text books, or proprietary research can be scientifically valid even if they are not formally “validated,” we are revising proposed § 111.60(d). Under final § 111.320(b) you must identify and use an appropriate “scientifically valid method” (rather than a “validated method”) for each established specification for which testing or examination is required to determine whether the specification is met.

However, we continue to recommend that you use tests and examinations that already have been validated when such tests are available.

(Comment 283) One comment specifically asks how much modification of a validated method is allowed before the method must be re-validated by the laboratory. The comment cites an example of moisture testing in which the testing method needs to be modified to provide a more valid moisture reading.

(Response) In the preamble to the 2003 CGMP proposal (68 FR 12157 at 12209), we recommended that, if you modify an officially validated method,

you document the reason for the modification and have data to show that the modified method produces results that are at least as accurate and reliable as the established method for the material being tested. We also recommended that you have complete records of any testing and standardization of laboratory reference standards, reagents, and standard solutions that you use in your laboratory operations. We are making no changes to these recommendations in this final rule.

(Comment 284) Several comments request the final rule incorporate by reference authoritative sources of compendial methods.

(Response) We decline this request for the reasons discussed in response to comments 193 and 196.

G. Appropriate Test Method Validation (Proposed § 111.60(b)(1)(v))

Proposed § 111.60(b)(1)(v) would require the laboratory control processes you establish and follow to include the use of appropriate test method validations. Because the final rule does not require that you use a validated method for any tests or examinations that you conduct, we are removing proposed § 111.60(b)(1)(v).

H. Under This Subpart, What Records Must You Make and Keep? (Final § 111.325)

Final § 111.325 sets forth the requirements for records that quality control personnel must make and keep.

1. Final § 111.325(a)

Final § 111.325(a) requires you to make and keep records required under subpart J in accordance with subpart P. Final § 111.325(a) derives from proposed § 111.60(b)(3), which would require you to keep laboratory

examination and testing records in accordance with proposed § 111.125.

Because final § 111.303 requires you to establish and follow written procedures for laboratory operations, the records you must make and keep under final § 111.325 are not limited to laboratory examination and testing records, but also include the written procedures. Final § 111.325(a) also includes editorial revisions associated with the reorganization and editorial revisions for consistency with the recordkeeping requirements in subparts P.

We did not receive comments specific to proposed § 111.60(b)(3).

2. Final § 111.325(b)(1)

The final rule includes a new requirement (final § 111.303) that you establish and follow written procedures for laboratory operations, including written procedures for the tests and examinations you conduct to determine whether specifications are met. Those written procedures are records. Therefore, final § 111.325(b)(1) requires you to make and keep a record of the written procedures for laboratory operations, including written procedures for the tests and examinations that you conduct to determine whether specifications are met.

3. Final § 111.325(b)(2)

Final § 111.325(b)(2) sets forth requirements for documenting that you followed the laboratory methodology established in accordance with this subpart. Final § 111.325(b)(2)(i) requires that the person who conducts the testing and examination document, at the time of performance, that laboratory methodology established in accordance with this subpart is followed. Final § 111.325(b)(2)(ii) requires that the documentation include the results of the testing and examination. Final § 111.325(b)(2) derives from proposed § 111.60(b)(2) with revisions associated with the reorganization.

(Comment 285) One comment states that, without appropriate documentation, there would be no assurance that the appropriate testing was indeed performed and that the product's identity, purity, quality, strength, and composition are what they are represented to be.

(Response) We agree and have retained the requirement in this final provision.

XVI. Comments on the Production and Process Control System: Requirements for Manufacturing Operations (Final Subpart K)

A. Organization of Final Subpart K

In the 2003 CGMP Proposal, the requirements for manufacturing operations were set forth in § 111.65. As shown in table 12 of this document, we are establishing the requirements for manufacturing operations in a distinct subpart (final Subpart K—Production and Process Control System: Requirements for Manufacturing Operations). In addition, we are incorporating some requirements from proposed § 111.74 relating to rejected components, dietary supplements, and packaging and labels into final subpart K. Table 12 lists the sections in final subpart K and identifies the proposed sections that form the basis of the final rule.

TABLE 12.—DERIVATION OF SECTIONS IN FINAL SUBPART K

Final Rule	2003 CGMP Proposal
§ 111.353 What are the requirements under this subpart K for written procedures?	N/A
§ 111.355 What are the design requirements for manufacturing operations?	§ 111.65(a)
§ 111.360 What are the requirements for sanitation?	§ 111.65(b)
§ 111.365 What precautions must you take to prevent contamination?	§ 111.65(c)
§ 111.370 What requirements apply to rejected dietary supplements?	§ 111.74

TABLE 12.—DERIVATION OF SECTIONS IN
FINAL SUBPART K—Continued

Final Rule	2003 CGMP Proposal
§ 111.375 Under this subpart K, what records must you make and keep?	N/A

B. Highlights of Changes to the Proposed Requirements for Manufacturing Operations

1. Revisions

The final rule:

- Applies to persons who manufacture, package, label, or hold dietary supplements unless subject to an exclusion in § 111.1 and
- Reflects changes relevant to this subpart that we are making to final subpart C concerning water standards.

2. Changes Made After Considering Comments

The final rule requires written procedures for manufacturing operations.

3. Revisions Associated With the Reorganization

The final rule sets forth in final § 111.90, rather than in subpart K, the requirements for in-process adjustments or reprocessing.

C. General Comments on Manufacturing Operations

(Comment 286) Some comments support proposed § 111.65 as a “good model” for an appropriate level of flexibility, noting that proposed § 111.65 clearly states the requirements and presents relevant factors that must be considered when determining how to best meet the requirements of the rule.

(Response) We acknowledge these comments and utilize many elements of proposed § 111.65 in final § 111.355.

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

(Final § 111.353)

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, final § 111.353, to require that you establish and follow written procedures for manufacturing operations.

E. What Are the Design Requirements for Manufacturing Operations? (Final § 111.355)

Final § 111.355 requires you to design or select manufacturing processes to ensure that product specifications are consistently met. Final § 111.355 derives from proposed § 111.65(a) which would require you to design or select manufacturing processes to ensure that dietary supplement specifications are consistently achieved. Final § 111.355 refers to “product specifications” rather than “dietary supplement specifications” to conform with final § 111.70(e). We have substituted the word “met” for “achieved” to comply with plain language initiatives and to be consistent with other provisions.

We did not receive comments specific to proposed § 111.65(a).

F. What Are the Requirements for Sanitation? (Final § 111.360)

Final § 111.360 requires you to conduct all manufacturing operations in accordance with adequate sanitation principles. Final § 111.360 derives from proposed § 111.65(b). We did not receive comments specific to proposed § 111.65(b).

G. What Precautions Must You Take to Prevent Contamination? (Final § 111.365)

Final § 111.365 requires you to take all necessary precautions during the manufacture of a dietary supplement to prevent contamination of components or dietary supplements. Final § 111.365 derives from proposed § 111.65(c)(1) through (c)(11).

1. Final § 111.365(a)

Final § 111.365(a) requires that the necessary precautions include performing manufacturing operations under conditions and controls that protect against the potential for growth of microorganisms and the potential for contamination. Final § 111.365(a) derives from proposed § 111.65(c)(1).

(Comment 287) One comment contends that the requirement in proposed § 111.65(c)(1) to protect “against the potential for growth of microorganisms,” does not take into account processes that have a kill step. The comment recommends that proposed § 111.65(c)(1) be revised to be more consistent with § 110.80(b)(2) and state, “performing manufacturing operations under such conditions and controls as are necessary to minimize the potential for the growth of undesirable microorganisms, or for the contamination of the product.”

(Response) We decline to modify final § 111.365(a) as requested by the comment because the provision accomplishes what is requested by the comment. We defined “microorganism” in the 2003 CGMP Proposal similar to how we describe “undesirable microorganisms” in § 110.3(i). Further, we decline to use the words “minimize the potential for growth” instead of “protect against the potential for growth” because the word “minimize”

suggests a lesser standard than “protect against” the potential for growth of microorganisms.

We would consider that you are not complying with the final rule if you do not perform manufacturing operations under conditions and controls that protect against the potential for growth of microorganisms and the potential for contamination, regardless of whether you use a kill step. Although a kill step may be necessary in some circumstances, it is not a substitute for conditions and controls that protect against the potential for growth of microorganisms and the potential for contamination. Therefore, we decline to make the change requested by this comment.

2. Final § 111.365(b)

Final § 111.365(b) requires that necessary precautions include washing or cleaning components that contain soil or other contaminants. Final § 111.365(b) is identical to proposed § 111.65(c)(2). We did not receive comments specific to proposed § 111.65(c)(2).

3. Final 111.365(c)

Final § 111.365(c) requires that the necessary precautions include using water that, at a minimum, complies with the applicable Federal, State, and local requirements and does not contaminate the dietary supplement when the water may become a component of the finished batch of dietary supplement.

The proposed requirements would set forth parallel requirements for water that is used in the manufacture of a dietary supplement for both your physical plant (proposed § 111.15(d)(2)) and for manufacturing operations (proposed § 111.65(c)(3)). Thus, proposed § 111.15(d)(2) would require that water that contacts components, dietary ingredients, dietary supplements, or any contact surface must, at a minimum, comply with the NPDW regulations prescribed

by the Environmental Protection Agency under 40 CFR part 141 and any State and local requirements.

As discussed in section VIII of this document (final § 111.15(e)(2) in subpart C), we are revising proposed § 111.15(d)(2) to require in the final rule that water, used in the manufacture of a dietary supplement in a manner such that the water may become a component of the dietary supplement, i.e., when such water contacts components, dietary supplements, or any contact surface, must, at a minimum, comply with applicable Federal, State, and local requirements and not contaminate the dietary supplement. Given the parallel nature of proposed § 111.65(c)(3) and proposed § 111.15(d)(2), we are revising proposed § 111.65(c) to be consistent with the revisions we are making to proposed § 111.15(d)(2) (final § 111.15(e)(2)).

Final § 111.365(c) also includes grammatical changes consistent with the structure of final § 111.365.

(Comment 288) One comment asks that the words “or equivalent quality water” be added to “water that meets the National Primary Drinking Water regulations” in proposed § 111.65(c)(3) to allow for ingredients manufactured in facilities outside the United States.

(Response) As stated in response to comment 91, dietary supplements manufactured in a foreign country would be subject to the requirements of this final rule. Although the Environmental Protection Agency NPDW regulations would not apply to a foreign manufacturer, the foreign manufacturer would need to use water that is of a standard required in this final rule and that achieves the same level of performance required of domestic manufacturers. The water used by the foreign facility must not contaminate the dietary supplement that is manufactured. We decline to add “or equivalent water

quality” because that would suggest domestic firms would not need to follow whatever Federal, State, and local requirements are applicable.

(Comment 289) One comment recommends that proposed § 111.65(c)(3) be revised to be consistent with proposed § 111.15(d)(1), which would require you to provide water that is safe and of adequate sanitary quality, at suitable temperatures, and under pressure as needed, in all areas where water is necessary for: (1) Manufacturing dietary ingredients or dietary supplements; (2) making ice that comes in contact with components, dietary ingredients, dietary supplements, or contact surfaces; (3) cleaning any surface; and (4) employee bathrooms and hand-washing facilities.

(Response) We do not agree with the comment that we should be consistent in the water requirement related to proposed § 111.15(d)(1) and the requirement in proposed § 111.65(c)(3). The requirement in proposed § 111.15(d)(1) describes a variety of manufacturing operations where water is used. For example, water that is safe and of adequate sanitary quality, as described in the proposed rule, for purposes of manufacturing dietary supplements or that comes into contact with a dietary supplement would be water that would have been required to comply with the requirement in proposed § 111.15(d)(2). Under the proposed rule and under the final rule, if such water is subject to Environmental Protection Agency NPDW, then the water must meet Environmental Protection Agency NPDW requirements at point of use. Proposed § 111.15(d)(1) has been revised and simplified in final § 111.15(e)(1) to require you to provide water that is safe and sanitary, at suitable temperatures, and under pressure as needed, for all uses where water does not become a component of the dietary supplement. Water that is safe and sanitary for cleaning the floor in a facility would not need to meet

standards for drinking water, but such water could not be a source of contamination of the dietary supplement. The standard “safe and sanitary” in final § 111.15(e)(1) allows some flexibility for the manufacturer in deciding what water it can use in various operations for which no other requirements in this final rule apply. The requirements of final § 111.365(c) are consistent with the changes in final § 111.15(e).

4. Final § 111.365(d)

Final § 111.365(d) requires that the necessary precautions you take during the manufacture of a dietary supplement to prevent contamination of components or dietary supplements include performing chemical, microbiological, or other testing, as necessary to prevent the use of contaminated components. Final § 111.365(d) derives from proposed § 111.65(c)(4).

(Comment 290) One comment asserts that requirements for testing belong in proposed § 111.25 (proposed requirements for equipment and utensils) rather than in proposed § 111.65 (proposed requirements for manufacturing operations).

(Response) In our discussion of proposed § 111.65(c)(4) in the 2003 CGMP Proposal (68 FR 12157 at 12210), we stated that you consider identifying those areas in the processing and production areas where chemical, microbial, or other forms of contamination are most likely to occur. We also stated that chemical, microbial, or other testing is necessary to identify areas where sanitation measures have not been adequate or where products may become adulterated. These remarks reflect that the proposed requirement in proposed § 111.65(c)(4) is directed to facilities rather than to equipment and utensils. For example, under proposed § 111.65(c)(4), we encouraged you to establish

a testing program that monitors levels of microorganisms at key places in your physical plant where you process and produce your products. Thus, we disagree with the comment that the testing requirements belong in proposed § 111.25 and are not making any changes in final § 111.365(d).

5. Final § 111.365(e)

Final § 111.365(e) requires that the necessary precautions you take during the manufacture of a dietary supplement to prevent contamination of components or dietary supplements include sterilizing, pasteurizing, freezing, refrigerating, controlling hydrogen-ion concentration (pH), controlling humidity, controlling water activity (a_w), or using any other effective means to remove, destroy, or prevent the growth of microorganisms, and prevent decomposition. Final § 111.365(e) derives from proposed § 111.65(c)(5).

(Comment 291) One comment asserts that only sanitary practices are needed to prevent microbial contamination or decomposition, and, therefore, requests that we clarify the processes listed in proposed § 111.65(c)(5) are optional.

(Response) We disagree with this comment. Good sanitary practices are important, but they are not the only precaution to take to prevent a component or dietary supplement from contamination with microorganisms. In the preamble to the 2003 CGMP Proposal, we gave the example of bovine colostrum, which is the lacteal secretion that precedes milk after a cow gives birth and is a substance that is used in dietary supplements. We also stated that we consider that bovine colostrum likely presents the same potential health risks as bovine milk, which can contain pathogenic organisms capable of causing diseases in man such as tuberculosis, undulant fever, or gastrointestinal disease and, thus, must be pasteurized (21 CFR 1240.61).

Under final § 111.365(e) you must sterilize or pasteurize bovine colostrums, or take other steps, to remove or destroy microorganisms that could be present in bovine colostrum. Under final § 111.365(e) we list various ways that, depending upon the particular situation, would be effective in removing, destroying, or preventing the growth of microorganisms and preventing decomposition. You must decide for your given operation what means to use to remove, destroy, or prevent the growth of microorganisms and prevent deterioration of your components and dietary supplements so that you ensure the quality of the dietary supplement.

(Comment 292) Some comments recommend adding “irradiating” to the list of practices to prevent the growth of microorganisms in proposed § 111.65(c)(5) similar to the industry CGMP provision, “Production and Process Controls,” section (d)(5), published in the 1997 ANPRM.

(Response) We decline to revise the provision as suggested by these comments. We are not adding “irradiating” to the list of practices because, at this time, irradiation of dietary ingredients and dietary supplements, as a means to reduce or eliminate microbial loads, is not permitted. CFSAN is currently reviewing the use of irradiation for the control of microbial contamination on dietary supplements and ingredients (including dietary ingredients) used in the manufacture of dietary supplements (68 FR 25048, May 9, 2003). If we authorize this use of irradiation you could then use irradiation in compliance with that rule to comply with final § 111.365(e) as an “other effective means.”

6. Final § 111.365(f)

Final § 111.365(f) requires that the necessary precautions you take during the manufacture of a dietary supplement to prevent contamination of

components or dietary supplements include holding components and dietary supplements that can support the rapid growth of microorganisms of public health significance in a manner that prevents the components and dietary supplements from becoming adulterated. Final § 111.365(f) derives from proposed § 111.65(c)(6). We did not receive comments specific to proposed § 111.65(c)(6).

7. Final § 111.365(g)

Final § 111.365(g) requires that the necessary precautions you take during the manufacture of a dietary supplement to prevent contamination of components or dietary supplements include identifying and holding any components or dietary supplements, for which a material review and disposition decision is required, in a manner that protects components or dietary supplements that are not under a material review against contamination and mixups with those under a material review. Final § 111.365(g) is substantially similar to proposed § 111.65(c)(7). We did not receive comments specific to proposed § 111.65(c)(7).

8. Final § 111.365(h)

Final § 111.365(h) requires that the necessary precautions you take during the manufacture of a dietary supplement to prevent contamination of components or dietary supplements include performing mechanical manufacturing steps (such as cutting, sorting, inspecting, shredding, drying, grinding, blending, and sifting) by any effective means to protect the dietary supplements against contamination. Final § 111.365(h) derives from proposed § 111.65(c)(8). Such steps must include consideration of: (1) Cleaning and sanitizing contact surfaces, (2) using temperature controls, and (3) using time controls.

(Comment 293) One comment suggests that the time controls required in proposed § 111.65(c)(8)(iii) are not always necessary.

(Response) As written, proposed § 111.65(c)(8) acknowledges that time controls are not always necessary, because the provision requires that you consider using time controls, and implement them if they are necessary to prevent contamination of components or dietary supplements. Final § 111.65(h) retains this same language.

9. Final § 111.365(i)

Final § 111.365(i) requires that the necessary precautions you take during the manufacture of a dietary supplement to prevent contamination of components or dietary supplements include using effective measures to protect against the inclusion of metal or other foreign material in components or dietary supplements. Compliance with this requirement must include consideration of the use of: (1) Filters or strainers, (2) traps, (3) magnets, or (4) electronic metal detectors. Final § 111.365(i) derives from proposed § 111.65(c)(9).

(Comment 294) One comment contends it is sufficient to require in proposed § 111.65(c)(9) that manufacturers inspect their equipment before and after use to determine if any piece is missing, and if so, the entire batch should be disposed of. The comment states metal detection devices are not 100 percent effective and that inspection of equipment before and after use would be preferable.

(Response) We disagree with the comment. As discussed in the 2003 CGMP Proposal, the purpose behind proposed § 111.65(c)(9) is to ensure that no metal or foreign material becomes a source of possible contamination and not to establish mechanisms to be used after contamination has or is suspected

to have occurred (68 FR 12157 at 12211). The source of metal contamination is not limited to manufacturing equipment. For example, metal contamination could occur through using utensils such as metal brushes during processing of natural products. It would be impractical to determine whether contamination has occurred by examining the brush.

10. Final § 111.365(j)

Final § 111.365(j) requires that the necessary precautions you take during the manufacture of a dietary supplement to prevent contamination of components or dietary supplements include segregating and identifying all containers for a specific batch of dietary supplements to identify their contents and, when necessary, the phase of manufacturing. Final § 111.365(j) derives from proposed § 111.65(c)(10). We did not receive comments specific to proposed § 111.65(c)(10).

11. Final § 111.365(k)

Final § 111.365(k) requires that the necessary precautions you take during the manufacture of a dietary supplement to prevent contamination of components or dietary supplements include identifying all processing lines and major equipment used during manufacturing to indicate their contents, including the name of the dietary supplement and the specific batch or lot number and, when necessary, the phase of manufacturing. Final § 111.365(k) derives from proposed § 111.65(c)(11).

(Comment 295) One comment suggests continuous processes should be excluded from the requirement in proposed § 111.65(c)(11) to identify specific batch or lot numbers. The comment explains that in continuous bulk operations for manufacturing dietary ingredients, the batch or lot number often

is not identified until after the materials have been blended and moved into a storage bin.

(Response) We are making no changes to proposed § 111.65(c)(11) in final § 111.365(k) because the comment describes a situation where the manufacturer is manufacturing a dietary ingredient, and the final rule does not apply to the manufacture of a “dietary ingredient” within the meaning of section 201(ff) of the act.

H. What Requirements Apply to Rejected Dietary Supplements? (Final § 111.370)

Final § 111.370 requires you to clearly identify, hold, and control under a quarantine system for appropriate disposition any dietary supplement that is rejected and unsuitable for use in manufacturing, packaging, or label operations. Final § 111.370 derives from proposed § 111.74 which would require that you 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. Because the requirements regarding components, packaging, and labels that are rejected and unsuitable for use are already set forth in final § 111.170, final § 111.370 addresses only the requirements for dietary supplements.

We did not receive comments specific to proposed § 111.74.

I. Under This Subpart, What Records Must You Make and Keep? (Final § 111.375)

In order to ensure that records are maintained as required under subpart P, we are adding a new § 111.375. This section requires that you make and

keep records of the written procedures you establish for manufacturing operations. These written procedures are required under final § 111.353.

XVII. Comments on the Production and Process Control System: Requirements for Packaging and Labeling Operations (Final Subpart L)

A. Organization of Final Subpart L

In the 2003 CGMP Proposal, the requirements for packaging and labeling operations were set forth in § 111.70. As shown in table 13 of this document, the final rule reorganizes the requirements related to quality control operations into a distinct subpart (final Subpart L—Production and Process Control System: Requirements for Packaging and Labeling Operations). Table 13 lists the sections in final subpart L and identifies the proposed sections that form the basis of the final rule.

TABLE 13.—DERIVATION OF SECTIONS IN FINAL SUBPART L

Final Rule	2003 CGMP Proposal
§ 111.403 What are the requirements under this subpart L for written procedures?	N/A
§ 111.410 What requirements apply to packaging and labels?	§ 111.70(a), (b)(6), and (f)
§ 111.415 What requirements apply to filling, assembling, packaging, labeling, and related operations?	§ 111.70(b)
§ 111.420 What requirements apply to repackaging and relabeling?	§ 111.70(d) and (e)
§ 111.425 What requirements apply to a packaged and labeled dietary supplement that is rejected for distribution?	§ 111.74
§ 111.430 Under this subpart L, what records must you make and keep?	§ 111.70(g) and (h)

B. Highlights of Changes to the Proposed Requirements for Packaging and Labeling Operations

1. Revisions

The final rule:

- Reflects that the final rule applies to persons who manufacture, package, label, or hold dietary supplements unless subject to an exclusion in § 111.1.
- Reflects that the labeling requirements of the rule address the operation of putting the label specified in the master manufacturing record on the final product.
- Clarifies the applicability of the rule to labeling operations.

2. Changes Associated With the Reorganization

We are moving to final § 111.260(k) in subpart I the requirements for the documentation, in the batch production record, of packaging and labeling operations (proposed § 111.70(g)).

3. Changes After Considering Comments

The final rule:

- Requires you to establish and follow written procedures for packaging and labeling operations.
- Provides for an exception to the requirements for label reconciliation for cut or rolled labels if a 100-percent examination for correct labels is performed by appropriate electronic or electromechanical equipment during or after completion of finishing operations.
- Clarifies the requirement for “retesting or re-examining” any repackaged or relabeled dietary supplements, i.e., consistent with final § 111.75(g) you must examine a representative sample of each batch of repackaged or relabeled

dietary supplements to determine whether repackaged or relabeled dietary supplements meet all specifications established in accordance with § 111.70(g).

C. General Comments on Proposed Requirements for Packaging and Labeling Operations

(Comment 296) Some comments assert that the proposed packaging and labeling requirements are unnecessarily stringent for dietary ingredients, because the potential for abuse is primarily at the final product stage.

(Response) To the extent that the comment is saying that a dietary ingredient manufacturer who manufactures, packages, labels, and holds a dietary ingredient that is further processed and incorporated into a dietary supplement by another person should not have to comply with the packaging and labeling requirements in subpart L, we agree. We are modifying the scope of the rule as to who is subject to the CGMP requirements, as discussed in section VI of this document (subpart A). The final rule applies to persons who manufacture, package, label, or hold dietary supplements unless subject to an exclusion in § 111.1.

(Comment 297) Several comments assert that it is imperative that a dietary supplement contain what it purports on its label. Some comments state that the amounts of ingredients listed on the label must accurately reflect what is in the package.

(Response) To the extent that the comments are suggesting that there need to be requirements for labeling operations as part of CGMP to ensure that the label applied to the dietary supplement is the label specified in the master manufacturing record for the finished product, we agree. To the extent that the comments suggest that CGMP requirements should ensure the quality of the dietary supplement manufactured, we also agree. If consumers believe that

dietary supplements contain the ingredients as labeled, as with any other product they purchase, then CGMP requirements should help to ensure that dietary supplements are manufactured consistently to ensure the quality of the dietary supplement and to help ensure the proper identity and amount of ingredients identified on the label.

D. General Comments on Requirements for What Must Be on the Product Label Rather Than for Labeling Operations

(Comment 298) Some comments express disappointment that the 2003 CGMP Proposal does not address product claims included on product labels. These comments state that, if FDA is not going to review label claims, it should, at a minimum, require the following statement be placed on dietary supplement products: "This product has not been reviewed for safety and efficacy by the FDA." These comments assert that such a statement should be included on all dietary supplement products, regardless of whether the product makes structure/function claims. These comments also recommend that dietary supplement labeling encourage consumers to share information about their use of the dietary supplements with their pharmacists and physicians and encourage consumers to seek the input of a health care provider if symptoms that prompted use of the dietary supplement are not resolved.

One comment requests we establish specific label content to include on dietary supplement labels. The comment asserts that the technology and mechanical tools exist to produce expanded labeling for dietary supplements efficiently and cost-effectively. The comment asserts that the content should include a complete listing of ingredients, relative percentages, batch or lot number, intended use, safety information, directions, and product information. Specifically, the comment supports the labeling recommendations of the U.S.

Department of Health and Human Services (HHS), Office of the Inspector General (OIG) "Dietary Supplement Labels: Key Elements," March 2003, publication no. OEI-01-01-00120, available at <http://oig.hhs.gov/oei/reports/oei-01-01-00120.pdf> (Ref. 34). The comment endorses the HHS/OIG recommendations, with the addition of batch or lot number on the label. The comment also endorses the OIG's proposed label presentation which calls for: (1) A standardized format with similar types of information in a similar order across supplements; (2) distinct product features to assist consumers in distinguishing supplements from other health care products; (3) readability, with language and visual cues that are easily understood by consumers; (4) balance to present information in a fair and balanced format that omits marketing and sales pitches; and (5) constructive use of space whereby innovative packaging is employed to expand label space.

Several comments address whether we should permit manufacturers to state on their products that the manufacturer of the product is in compliance with FDA CGMP requirements. Several comments assert that a CGMP statement on labels should not be allowed. These comments assert that the proposed "made in a CGMP facility" language is fraught with potential misuse, and that the potential for confusion is overwhelming. These comments state that the rule also should be modified to exclude other similar statements such as "produced using good laboratory practices," "produced using good practices," or "produced in compliance with USP good manufacturing practices." According to these comments, similar statements currently appear on dietary supplement labels and also may be misleading. These comments assert that CGMP requirements are not voluntary and should not be marketed as such.

Some comments state that a voluntary label statement that a dietary supplement complies with CGMP should be allowed. According to these comments, there are several third party organizations such as USP and National Nutritional Foods Association (NNFA) that have proposed or established CGMP requirements as rigorous as, or more rigorous than, those proposed by FDA. These comments assert that a voluntary statement that characterizes the nature of the GMP compliance should be allowed.

(Response) The comments related to requests about specific label content, such as ingredient listing, relative percentage of ingredients, intended use, safety information, label format, use of label space, and directions and product information are outside the scope of this final rule. Further, with respect to requiring specific statements about dietary supplement product, such as, "This product has not been reviewed for safety and efficacy by the FDA," or "This product has been produced using good manufacturing practice," we have stated previously that the manufacturer is responsible for ensuring that any voluntary labeling statements on its dietary supplement products are truthful and not misleading (68 FR 12157 at 12164). We would review the lawfulness of such statements under sections 403(a)(1) and 201(n) of the act.

We did not propose to require any specific statements. We stated that an unqualified statement such as "produced in compliance with dietary supplement current good manufacturing practice requirements," without more, could suggest a product may be safe and effective or somehow superior to other dietary supplement products that are subject to the same CGMP requirements (id.). Further, we stated that such a statement would likely be considered misleading by us under sections 403(a)(1) and 201(n) of the act, but that including language clarifying to consumers that all dietary supplements must

be manufactured in compliance with CGMP requirements and that such compliance does not mean that the dietary supplement is safe or effective may be a way to cure that unqualified statement (*id.*). Thus, we are not prohibiting voluntary statements on the dietary supplement label, provided that such statements are truthful and not misleading.

(Comment 299) Some comments assert that the labeling standards found in the 2003 CGMP Proposal should be uniformly applied across manufacturers, regardless of size, because consumers are unlikely to differentiate between small companies and large ones when selecting dietary supplements. These comments assert that we should, therefore, only allow 1 year for labeling compliance for all manufacturers regardless of their size.

Some comments assert that small manufacturers are more likely to suffer competitively if their labels lack important ingredient and other information relative to labeling employed by their larger competitors. These comments argue that enhanced labeling is a cost-effective packaging feature and should not represent a significant cost burden when outsourced to a qualified print-packaging vendor. Moreover, labels already represent a budgeted cost item for dietary supplement producers. Labels with additional content would add little to manufacturer overhead.

(Response) These comments may have misinterpreted the 2003 CGMP Proposal. The CGMP requirements do not impose any requirements for the specific content of the label. We discuss the requirements necessary to determine the complete manufacturing history and control of a packaged and labeled dietary supplement through distribution in this subpart in our discussion on final § 111.410(d). To the extent that businesses with fewer than 500 employees want to comply with the CGMP requirements for labeling

operations in a shorter timeframe than what we are allowing in this final rule, such businesses may do so. However, to assist businesses with fewer than 500 employees in complying with dietary supplement CGMPs, we are giving businesses with fewer than 500 but 20 or more employees a compliance date of 24 months after the date of publication of this final rule, and we are giving businesses with fewer than 20 employees a compliance date of 36 months after the date of publication of this final rule.

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

(Final § 111.403)

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 § 111.403 requires you to establish and follow written procedures for packaging and labeling operations. Under final 111.430(b), relating to records you must make and keep, we require that you make and keep records of such written procedures.

F. What Requirements Apply to Packaging and Labels? (Final § 111.410)

1. Final § 111.410(a)

Final § 111.410(a) requires that you take necessary actions to determine whether the packaging for dietary supplements meets specifications so that the condition of the packaging will ensure the quality of your dietary supplements. Final § 111.410(a) is similar to proposed § 111.70(a) which would require you to take necessary actions to ensure that each packaging container for holding dietary ingredients or dietary supplements meets specifications so that the

condition of the packaging container will not contaminate your dietary supplements or cause them to deteriorate. We have made changes to be consistent with final § 111.70 and the definition of “quality” by substituting the phrase “ensure the quality of your dietary supplement” instead of using the words “contamination” and “deterioration” which would be encompassed in the definition of “quality.” We are deleting the words “container” and “holding” from final § 111.410(a) to emphasize that all packaging must meet specifications and ensure the quality of the dietary supplement.

(Comment 300) One comment requests the removal of the word “each” from proposed § 111.70(a) because the inclusion of the word mandates that each and every container, rather than a representative sample, be inspected.

(Response) Because the final rule only requires the use of representative samples to ensure compliance, as provided in final § 111.80, to reduce the potential for confusion, we are deleting the word “each” and making associated grammatical revisions.

(Comment 301) Some comments request we clarify our expectations under proposed § 111.70(a) with respect to substantiating that packaging containers meet specifications and will not contaminate dietary supplements. The comments assert that it is not necessary for a manufacturer to test these types of products proactively, and that a continuing product guarantee combined with a statement of intended use from the manufacturer of the packaging material should suffice to meet the proposed requirements. The comments assert this is consistent with expected practice in other industries that FDA regulates.

(Response) Final § 111.410(a) reiterates the requirement of final § 111.70(d) to establish packaging specifications and the requirement of final § 111.75(f)(1)

to determine whether packaging specifications are met. Under final § 111.75(f)(1), to determine whether packaging meets its specifications, you must conduct a visual identification of the containers and closures and review the supplier's invoice, guarantee, or certification. Thus, the final rule does not require that you test packaging proactively, and does allow you to rely on documentation such as a continuing product guarantee combined with a statement of intended use from the manufacturer of the packaging.

As we discussed in the preamble to 2003 CGMP Proposal (68 FR 12157 at 12212), proposed § 111.70(a) would require you to take into account factors such as whether your product is sensitive to light when setting specifications for packaging. Other factors to consider include whether your product is sensitive to moisture or could interact with certain kinds of packaging. (For other requirements related to packaging, see final §§ 111.70(d), (f), (g), and 111.160.)

2. Final § 111.410(b)

Final § 111.410(b) requires you to control the issuance and use of packaging and labels and reconciliation of any issuance and use discrepancies, except that label reconciliation is not required for cut or rolled labels if a 100-percent examination for correct labels is performed by appropriate electronic or electromechanical equipment during or after completion of finishing operations. Final § 111.410(b) derives from proposed § 111.70(f)(1) which would require you to control the issuance and use of packaging and labels and reconciliation of any issuance and use discrepancies.

(Comment 302) Some comments assert that comprehensive label reconciliation should not be required if appropriate electronic controls are instituted to ensure that correct labels are used during labeling operations. The

comments state this alternative is permitted for labeling operations for drug products, which are generally identical or similar in nature to labeling operations for dietary supplements. As such, the comments assert that the same flexibility should be afforded to dietary supplement manufacturers.

(Response) We agree with these comments and the revisions are reflected in final § 111.410(b) (proposed § 111.70(f)(1)).

3. Final § 111.410(c)

Final § 111.410(c) requires you to examine, before packaging and labeling operations, packaging and labels for each batch of dietary supplement to determine whether the packaging and labels conform to the master manufacturing record. Final § 111.410(c) derives from proposed § 111.70(f)(2). We did not receive comments specific to proposed § 111.70(f)(2).

4. Final § 111.410(d)

Final § 111.410(d) requires you to be able to determine the complete manufacturing history and control of the packaged and labeled dietary supplement through distribution. We are revising the language of proposed § 111.70(b)(6) and including in final § 111.410 the similar requirement stated in proposed § 111.70(b)(6). Section 111.410 is where we chose to place this requirement because it is likely that you will affix the batch, lot, or control number that you used for the finished batch of dietary supplement on the immediate container or on the product label as the means to trace the product through distribution, although this is not required. Other means are acceptable besides the use of a batch, lot, or control number.

(Comment 303) Some comments assert that we do not propose in the 2003 CGMP Proposal the affixing of a lot number to the container of product marketed to the consumer. These comments assert that all the recordkeeping

in the 2003 CGMP Proposal is of little value unless issues can be traced back from the individual container, perhaps received from a customer complaint, to a specific batch. These comments state that such labeling should be a requirement.

(Response) We agree that it is necessary to be able to trace a dietary supplement in distribution to a specific batch or lot of product. We disagree that we did not provide any requirements in the 2003 CGMP Proposal that would require you to be able to trace a distributed dietary supplement to a specific batch or lot.

In proposed § 111.70(b)(6) we stated that a batch, lot, or control number is necessary for you to trace the manufacturing history for a particular batch, which will help you investigate and correct any safety problems for a batch or to recall a dietary supplement. We discussed the fact that, without such a batch, lot, or control number, consumers would be unable to determine which product was the subject of a recall and they would not know which product to stop using, or there would be a need to recall more product than otherwise may be necessary (68 FR 12157 at 12212).

We also proposed several other requirements related to the need to be able to trace the components, packaging, and labeling used in the manufacture of a dietary supplement with the distributed dietary supplement. Under proposed § 111.40(a) (with respect to components and dietary supplements) and proposed § 111.40(b)(3) (with respect to packaging and labeling) we would require you to identify each lot of product received in a shipment in a manner to allow you to trace the shipment lot to the dietary supplement manufactured and distributed. In the preamble to the 2003 CGMP Proposal (68 FR 12157 at 12202), we stated that using a unique identifier throughout the

manufacturing process will make it possible to track and account for components and dietary supplements received to any necessary investigation of consumer complaints. In proposed § 111.50(c)(1) we provided that the batch production record must include a batch, lot, or control number, and in proposed § 111.50(c)(5) we provided that the batch production record must include the shipment lot unique identifier of each component, dietary ingredient, dietary supplement, packaging, and label used. Further, in proposed § 111.85(d), we required that you conduct an investigation if a returned dietary supplement implicates associated batches. Thus, we proposed to require that you be able to trace a dietary supplement through distribution. However, we did not require you to use a specific mechanism, such as affixing a batch, lot, or control number to the immediate container or product label. Under the 2003 CGMP Proposal, the manufacturer would have flexibility to determine the method to trace its product in distribution to the batch, lot, or control number assigned to the finished batch or lot of dietary supplement.

In final § 111.415(f), we require you to assign a batch, lot, or control number to: (1) Each lot of packaged and labeled dietary supplement from a finished batch of dietary supplement and (2) each lot of dietary supplement, from a finished batch of dietary supplement, that you distribute to another person for packaging or labeling. We do not require you to affix this batch, lot, or control number to the immediate container or the product label. Instead, we provide flexibility for you to determine how you track the batch, lot, or control number you assign to each lot of packaged and labeled dietary supplement from a finished batch of dietary supplement, and each lot of dietary supplement from a finished batch of dietary supplement you distribute to another person for packaging or labeling, to distributed dietary supplements.

To clarify that we do not require you to affix a batch, lot, or control number on the immediate container or product label, final § 111.410(d) provides that you must be able to determine the complete manufacturing history and control of the packaged and labeled dietary supplement through distribution by a method of your choice. For example, a dietary supplement manufacturer may make one type of product that it distributes to a select few customers and may be able to trace its dietary supplement using dates on distribution records to such customers, or may use different containers or labeling, other than a batch, lot, or control number that is affixed to the label.

We are retaining the use of a unique identifier in final §§ 111.155(d), 111.160(d), and 111.260(a), (d), and (k). These requirements relate to the tracking of a component, packaging, labeling, or dietary supplement throughout the manufacturing process. The use of a batch, lot, or control number or other unique identifier, as required, for product in the manufacturing process is needed for tracking components, packaging, and labels used to manufacture, package, or label a dietary supplement so that once a batch is identified, the components, packaging, and labels used in a batch will also be known. But by contrast, when the distribution of a final product may be distributed to a few select customers, or where every unique batch is placed in a different type of container, there may not be a need to use batch, lot, or control numbers affixed to the immediate container or product labels to be able to trace the product.

This final rule will enhance the benefits of the new statutory requirement for mandatory reporting to FDA of serious adverse events as the 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.

This final rule will facilitate the additional traceback activities taking place as a result of the additional serious adverse events discovered through mandatory reporting. We will evaluate such mandatory reports for patterns or “signals” of problems with particular products so that further harm to consumers may be prevented by removing the products and, in some cases, related products from the marketplace. This cannot be done without first quickly and accurately identifying the products of interest. To efficiently determine which specific products or group of products are associated with the serious (or non-serious) adverse event report, traceback ability is crucial. This final rule includes requirements that will provide the information needed to quickly and accurately conduct a sufficient traceback. The provisions that require maintenance of records for production processes include records such as batch records, unique identifiers, and master manufacturing records. The recordkeeping provisions of this final rule give us access to those records, so we will have an enhanced ability to investigate the serious adverse events reported to us, using records such as information on ingredients, processing, storage, composition, and distribution. 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.

G. What Requirements Apply to Filling, Assembling, Packaging, Labeling, and Related Operations? (Final § 111.415)

Final § 111.415 requires that you fill, assemble, package, label, and perform other related operations in a way that ensures the quality of the dietary supplement and that the dietary supplement is packaged and labeled as specified in the master manufacturing record. Final § 111.415 also requires that

you do these functions using any effective means you choose, including: (1) Cleaning and sanitizing all filling and packaging equipment, utensils, and dietary supplement packaging, as appropriate; (2) protecting manufactured dietary supplements from contamination, particularly airborne contamination; (3) using sanitary handling procedures; (4) establishing physical or spatial separation of packaging and label operations from operations on other components and dietary supplements to prevent mixups; (5) identifying, by any effective means, filled dietary supplement containers that are set aside and held in unlabeled condition for future label operations, to prevent mixups; (6) assigning a batch, lot, or control number to each lot of packaged and labeled dietary supplement from a finished batch of dietary supplement and each lot of dietary supplement from a finished batch of dietary supplement that you distribute to another person for packaging or labeling; (7) examining a representative sample of each batch of the packaged and labeled dietary supplement to determine whether the dietary supplement meets specifications established in accordance with final § 111.70(g); and (8) suitably disposing of labels and packaging for dietary supplements that are obsolete or incorrect to ensure that they are not used in any future packaging and labeling operations.

Final § 111.415 derives from proposed § 111.70(b). We revised the section to be consistent with other revisions.

(Comment 304) Some comments request clarification as to what specifications we are referring to in proposed § 111.70(b)(7). The comments state that if we are referring to specifications required by proposed § 111.35(e), then we should indicate so in any final rule. The comment asserts that, if we intend this provision to mean that persons who simply package, label, and