

established by a qualified person and is “adequate under the conditions of manufacture for a given product to achieve commercial sterility” (§§ 113.3 and 113.83). “Commercial sterility” of thermally processed food means a condition achieved by applying heat to render the food free of certain microorganisms (§ 113.3). Part 113 requires that supervisors satisfactorily complete training at a school approved by FDA (§ 113.10).

Part 113 also contains extremely detailed requirements on equipment and procedures. For example, each vessel used for pressure processing in steam must be equipped with a mercury thermometer that is tested for accuracy at least once a year, or more frequently if necessary, to ensure its accuracy (§ 113.40(a)(1)). Critical factors (variation of which may affect the attainment of commercial sterility) must be specified in the scheduled process and must be measured and recorded on processing records frequently enough to ensure that the factors are within the specified limits (at least every 15 minutes) (§§ 113.40(a)(13) and 113.83). Observations and measurements of certain operating conditions must be made and recorded at intervals of sufficient frequency to ensure that commercial sterility of the food product is being achieved (at least every hour) (§ 113.40(g)(2)(ii)(c)). There must also be a system to stop packaging operations (or to segregate products) when the packaging conditions fall below scheduled processes (§ 113.40(g)(2)(ii)(b)). Regular observations of container closures are required to be made and recorded (§ 113.60). Each container must be coded “to enable ready identification of lots during their sale and distribution” (§ 113.60(c)).

Before using raw materials and ingredients susceptible to microbiological contamination, the low-acid food processor must ensure that they are “suitable for use in processing low-acid food” (§ 113.81(a)). Complete records covering

all aspects of the establishment of the scheduled process and of certain confirmation tests must be maintained permanently (§ 113.83). Scheduled processes must be readily available to any duly authorized FDA employee (§ 113.87(a)). Whenever any process is less than the scheduled process or when critical factors are not in control, the low-acid food must be reprocessed or set aside for further evaluation as to public health significance (§ 113.89). Unless the evaluation demonstrates that the product is free of microorganisms of potential public health significance, the product either must be reprocessed to render it commercially sterile or destroyed (§ 113.89).

All process deviations involving a failure to satisfy the minimum requirements of the scheduled process must be recorded and kept in a separate file detailing the deviations and actions taken (§ 113.89). Detailed information on processing and production must be entered on forms (§ 113.100(a)). Not later than 1 working day after the actual process, and before the food is shipped or released for distribution, a qualified representative of management must review all processing and production records for completeness and to ensure that the product was subjected to the scheduled process (§ 113.100(b)). Records to identify the initial distribution of the finished product must be kept to facilitate segregation of lots that may have become contaminated or otherwise rendered unfit for their intended use (§ 113.100(d)). Records must be maintained at the processing plant for at least 1 year after the date of manufacturing and at a reasonably accessible location for another 2 years (§ 113.100(e)).

Similarly, the CGMP regulation for acidified food in part 114 requires supervision by personnel trained at an FDA-approved school (§ 114.10); manufacturing in accordance with a scheduled process established by a

qualified person (§§ 114.80 and 114.83); processing sufficient to destroy the vegetative cells of certain microorganisms (§ 114.80(a)(1)); sufficient control, including frequent testing and recording of results, to ensure that the finished hydrogen-ion concentration (pH) values are not higher than 4.6 (§ 114.80(a)(2)); testing and examinations of containers to ensure that the food is suitably protected from leakage or contamination (§ 114.80(a)(4)); and coding to enable ready identification of lots during their sale and distribution (§ 114.80(b)).

Whenever any acidified food process operation deviates from the scheduled process or the pH of the finished product exceeds 4.6, the processor must reprocess it, process it under part 113 requirements, or set it aside for evaluation as to any potential public health significance (§ 114.89). Unless the evaluation demonstrates that the food has undergone a process that has rendered it safe, the food must be fully reprocessed to render it safe or be destroyed (§ 114.89).

A record must be made of the procedures used in the public health evaluation and the results of the evaluation (§ 114.89). Records must be kept of examinations of raw materials, packaging materials, and finished products, and of suppliers' guarantees or certifications that verify compliance with our regulations (§ 114.100(a)). Processing and production records showing adherence to scheduled processes must be maintained and must have sufficient additional information such as product code, date, container size, and product, to permit a public health hazard evaluation of the processes applied to each lot, batch, or other portion (§ 114.100(b)). Departures from scheduled processes having a possible bearing on public health or the safety of the food must be recorded and kept in a separate file or log, along with the action taken to rectify the departure and the product disposition (§ 114.100(c)). Records must be kept

identifying initial distribution of the finished product to facilitate segregation of lots that may have become contaminated or otherwise unfit for their intended use. Copies of certain required records must be kept at a reasonably accessible location for 3 years from the date of manufacture (§ 114.100). The criteria in the part 114 regulation, as well as those in part 110, apply in determining whether an article of acidified food is adulterated under section 402(a)(3) of the act in that it has been manufactured under such conditions that it is unfit for food or under section 402(a)(4) of the act in that it has been prepared, packed, or held under insanitary conditions whereby it may have become contaminated with filth, or whereby it may have been rendered injurious to health (§ 114.5).

Many provisions of parts 113 and 114 also serve as models for provisions in the dietary supplement final rule. In many instances, the analogous provision in the dietary supplement final rule allows more flexibility in the means to achieve the goal. For example, under final § 111.13 qualified personnel must be assigned to supervise the manufacturing, packaging, labeling, or holding of dietary supplements. Although the supervisor must be qualified by education, training, or experience to supervise, the more restrictive requirement of parts 113 and 114 to attend an FDA-approved school is not included. The “scheduled process” for low-acid and acidified food manufacturing, processing, and packing is analogous to the required “system of production and process controls” that dietary supplement manufacturers must design and implement (final §§ 111.55 and 111.60(a)). Similarly, the “critical factors” required to be specified in the scheduled process for low-acid and acidified foods are akin to the “specifications” that dietary supplement manufacturers must establish for certain points in the

manufacturing process (final § 111.70). Just as low-acid food processors must establish procedures to ensure that ingredients are suitable for use, so too must dietary supplement manufacturers establish component and finished product specifications (final § 111.70(b) and (e)). Just as containers for acidified food must ensure suitable protection from contamination, packaging that comes into contact with dietary supplements must be safe and suitable for use (final § 111.70(d)). Dietary supplement in-process points, like the “critical factors” for low-acid and acidified food, must be monitored to detect any deviation or unanticipated occurrence that may result in adulteration (final § 111.75(b)(2)).

Rejected dietary supplements must also be held under quarantine (final §§ 111.370 and 111.425); dietary supplements which have been reprocessed, treated, or which have had in-process adjustments must meet all established product specifications and be approved before release (final § 111.90(c)). Similar to coding low-acid or acidified foods, dietary supplements must have assigned batch, lot, or control numbers (final § 111.415(f)). The design, calibrations, and cleaning of equipment and utensils must also result in the equipment and utensils being suitable for their intended uses and not result in contamination of components or dietary supplements (final § 111.27). Written procedures for the various controls are required (see, e.g., final §§ 111.8, 111.25, and 111.103), and required written records (see, e.g., final §§ 111.14, 111.23, 111.35, and 111.95) must be kept for 1 year past the shelf life date, if shelf life dating is used, or 2 years after the date of distribution of the last associated batch of dietary supplement (final § 111.605). All required dietary supplement CGMP records must be readily available for inspection and copying by FDA (final § 111.610(a)).

Finally, the bottled water CGMP regulation was promulgated to ensure the safety and sanitary quality of these products, which include all water processed and bottled for human consumption (38 FR 32563, November 26, 1973). The criteria in part 129, as well as in part 110, apply in determining whether the facilities, methods, practices, and controls used to process, bottle, hold, and ship bottled drinking water conform with good manufacturing practice “to assure that bottled drinking water is safe and that it has been processed, bottled, held, and transported under sanitary conditions” (§ 129.1). Part 129 requires plant construction and design features, such as a separate bottling room and an enclosed room for washing and sanitizing containers, to protect against contamination (§ 129.20). All plant equipment and utensils must be suitable for their intended use (§ 129.40(a)).

Both the product water supply and the operations water supply must be of a “safe, sanitary quality” in conformance with “the applicable laws and regulations of the government agency or agencies having jurisdiction” (§ 129.35(a)). Samples of source water must be analyzed at least once a year for chemical contaminants and once every 4 years for radiological contaminants (§ 129.35(a)(3)). Source water from other than a public water system must be sampled and analyzed for microbiological contaminants at least once a week (*id.*). The product water-contact surfaces of all containers and equipment must be clean and adequately sanitized and protected from contamination (§ 129.37(a) and (b)). Filling, capping, closing, sealing, and packaging of containers must be done so as to preclude contamination of the water (§ 129.37(d)). All product water contact surfaces must be nontoxic and in compliance with section 409 of the act (21 U.S.C. 348) (concerning food additives) (§ 129.40(a)(2)).

Numerous production processes and controls for bottled water are also required. For example, all treatment of product water must be effective in accomplishing its intended purpose and in accordance with section 409 of the act (§ 129.80(a)). The treatment processes must be performed with equipment and substances that will not adulterate the product (§ 129.80). Product water samples must be taken before bottling and analyzed as often as necessary to assure uniformity and effectiveness of the processes performed by the plant (§ 129.80(a)). Cleaning and sanitizing solutions must be sampled and tested to assure adequate performance (§ 129.80(c)).

Each unit package from a batch or segment of continuous production run must be identified by a production code (§ 129.80(e)). The plant must maintain information on the kind of product, volume, date, lot code, and distribution of finished product to wholesale and retail outlets (id.). During the process of filling, capping, or sealing the containers, performance must be monitored and the filled containers inspected to assure that they are sound, properly capped or sealed, and coded and labeled (§ 129.80(f)). All containers and closures must be sampled and inspected to ascertain that they are free from contamination (id.).

To assure that the plant's production of bottled water complies with applicable standards, laws, and regulations, the plant must analyze product samples at specified intervals (§ 129.80(g)). The methods used to analyze the samples must be approved by the government agency with jurisdiction (§ 129.80(g)(3)). Records of the date of sampling, type of product sampled, production code, and results of analysis must be maintained (§ 129.80(g)(3)). All required records must be maintained at the plant for at least 2 years

(§ 129.80(h)) and be available for official review by FDA at reasonable times (id.).

Provisions of the bottled water CGMP regulation also serve as a model for provisions of the dietary supplement CGMP regulation. For example, water that is used in a manner such that the water may become a component of a dietary supplement must at a minimum comply with applicable Federal, State, and local requirements and not contaminate the dietary supplements (final §§ 111.15(e)(2) and 111.365(c)). Precautions that must be taken to prevent contamination of components or dietary supplements include performing chemical, microbiological, or other testing (final § 111.365(d)). Filling, assembling, packaging, labeling, and related operations must be performed to protect the dietary supplement against adulteration (final § 111.415). Equipment and utensils must be suitable for their intended use (final § 111.27(a)). Safe and adequate cleaning compounds and sanitizing agents must be used (final § 111.15(c)(1)). Representative samples of each batch must be examined to ensure that the product meets established specifications (final § 111.415(g)). Each lot of packaged and labeled dietary supplement must be assigned a batch, lot, or control number (final § 111.415(f)).

Moreover, our interpretation of permissible requirements for the dietary supplement CGMP regulation is also consistent with the use of the terms “good manufacturing practice” and “current good manufacturing practice” in section 402(g) of the act. Although these terms are not defined in the act, GMP is generally used to refer to methods used in, and the facilities and controls used for, product manufacturing and related activities.⁵ The umbrella food CGMP

⁵Although the act does not define “current good manufacturing practice,” the term is used elsewhere in the statute (see, e.g., sections 501(a)(2)(B) (drug CGMP) and 520(f)(1)(A) of the act (device CGMP) (21 U.S.C. 351(a)(2)(B) and 21 U.S.C. 360j(f)(1)(A), respectively). Case law supports the agency’s view that “current” does not mean “actually prevailing manufacturing practice” in an industry and that such a practice need not be accepted by

regulation, for example, defines the “plant” covered by the requirements of that regulation as the facility used for, or in connection with, “the manufacturing, packaging, labeling, or holding of human food” (§ 110.3(k)). As we have described in detail, the objectives of the existing food CGMP regulations and the precise means (or requirements) used to achieve the objectives vary depending on the particular hazards and characteristics of the products and their manufacturing. For example, the umbrella food CGMP regulation is specifically designed to ensure that food is manufactured, processed, packed, and held under sanitary conditions and that the food is safe, clean, and wholesome. Low-acid and acidified food CGMP requirements focus on facilities, methods, practices, and controls to protect the public health against the particular risks of microbial contamination from these foods. The infant formula CGMP regulation is aimed at ensuring both the safety and nutritional potency of these special foods. Infant formula is often the sole item in the diet. An infant formula that does not meet the requirements for nutritional potency may cause a hazard to the health of the infant (see 61 FR 36154, July 9, 1996). The bottled water CGMP regulation embodies requirements for facilities, methods, practices, and controls used in processing, bottling, holding, and shipping of bottled water to ensure its safety and sanitary quality.

Like the food CGMP regulations after which they are modeled, the dietary supplement CGMP final rule contains criteria for facilities, methods, practices, and controls used in manufacturing, packaging, labeling, or holding dietary supplements to ensure the quality of the dietary supplement. Quality includes

a majority of manufacturers (*National Ass’n of Pharmaceutical Mfr’s v. Department of Health and Human Services*, 586 F. Supp. 740, 752 (S.D.N.Y. 1984)). Nevertheless, the requirements of this final rule embody current practices of many food and dietary supplement manufacturers, as reflected in the comments supporting the provisions of the proposed rule.

consistently meeting the established specifications for identity, purity, strength, and composition of the dietary supplement and limits on contaminants, in addition to manufacturing the dietary supplement under conditions to prevent adulteration. As Congress recognized in DSHEA, identity, purity, strength, and composition are essential characteristics for dietary supplements (see, e.g., section 403(s)(2) of the act (a dietary supplement is misbranded if its labeling fails to list the name and quantity of each dietary ingredient and if it fails to have the identity and strength or the quality, purity, or compositional specifications it is represented to meet)). Yet without information about the identity, purity, strength, or composition, the manufacturer could not know the final contents of the dietary supplements it manufactures or whether its processes are reliably and consistently producing the correct combination and amounts of ingredients in a dietary supplement. Accordingly, the final rule requires a manufacturer to establish specifications for the identity, purity, strength, and composition and for limits on contaminants of the dietary supplements it manufactures and ensure that such specifications are consistently met in the finished batch of dietary supplement (§ 111.75(e)). Dietary supplements, like infant formula, are relied upon by consumers not only to be safe, but also in many instances to provide specific and important claimed health benefits (see, e.g., section 403(r) of the act). In the preamble to the 2003 CGMP Proposal, we discussed a number of examples illustrating adulteration and improper formulation of dietary supplements caused by manufacturing, packaging, or holding practices (68 FR 12157 at 12162 and 12163). These dietary supplement CGMP requirements will help to protect consumers against similar types of adulteration and against reliance on products that are not properly formulated.

Generally recognized principles underlying CGMP also support our interpretation of section 402(g) of the act. Our interpretation of permissible CGMP regulations is reasonable based on recognized principles for controlling the quality of manufactured products in general (Ref. 9). As many comments asserted, if the dietary supplement CGMP requirements are to be meaningful, they must ensure quality in the finished product (see, for example, the discussion in section X of this document of comments regarding the production and process control system). Controls to ensure quality include planning processes to determine desired product features or characteristics, a system of controls to ensure that the desired product will be consistently produced, and making necessary improvements to the process (section 2.6 of Ref. 9). Manufacturers must plan what they intend to produce, institute adequate controls to achieve the desired outcome, and ensure that the controls work so that the desired outcome is consistently achieved. If the outcome is not consistently achieved, corrective actions need to be implemented in order to reach the desired outcome.

This final rule, like the other food CGMP regulations, embodies the basic concepts of controlling quality, i.e., planning, control, and improvement. As discussed earlier in the “Overview of CGMP” (section III.A of this document), we have defined the term “quality” for this dietary supplement CGMP regulation to mean “that the dietary supplement consistently meets the established specifications for identity, purity, strength, and composition and has been manufactured, packaged, labeled, and held under conditions to prevent adulteration under section 402(a)(1), (a)(2), (a)(3), and (a)(4) of the Federal Food, Drug, and Cosmetic Act.” Identifying the desired characteristics of identity, purity, strength, and composition of a dietary supplement, as

required in this final rule, is an essential part of the planning process to manufacture a dietary supplement. Without identifying specifications for each of these characteristics of a dietary supplement, it is not possible to control for, and repeatedly and reliably produce, the desired end product. Similarly, requirements for batch testing ensure that there is consistency from batch to batch. Packaging and labeling requirements ensure that suitable packaging is used and that the label identified in the master manufacturing record for the product is placed on the finished product. In addition, requirements related to consumer complaints help to ensure that manufacturers are made aware of problems related to their manufacturing processes, including those that may result in illness or injury, so that they can take corrective actions to prevent any future problems from occurring. The procedures for production and process control in this final rule also include as key elements measures to prevent contamination that could adulterate the product. Requirements to protect against contamination during the manufacturing, packaging, labeling, and holding operations help ensure that this aspect of "quality" is also achieved for dietary supplements. In sum, this final rule embodies principles for controlling quality through requirements designed to ensure both that the dietary supplement meets its established specifications for identity, purity, strength, and composition and that it is not adulterated.

The dietary supplement CGMP requirements are also reasonable because they take into consideration the different product forms in which these products will be manufactured. Unlike conventional foods, such as fruit, vegetables, cereals, and dairy products, dietary supplements will be sold in tablet, capsule, powder, or softgel form. They may also be sold as a concentrate, metabolite, constituent, or extract of a vitamin, mineral, herb, botanical, or

dietary substance. Because dietary supplements are often sold in different forms than conventional foods, different processes and controls are needed to manufacture dietary supplements than to manufacture conventional foods. For example, equipment must be able to manufacture dietary supplements in tablet or softgel form. Therefore, the final rule requires that controls be established to ensure that the equipment functions in accordance with its intended use (final § 111.30(e)) and will consistently manufacture a product in whatever form is desired. Consistent with basic CGMP principles, ensuring the quality of the dietary supplement product requires that the manufacturer establish precisely what it will produce (specifications for its product), how it will make the product (processes), and which process controls and tests it will use to ensure reliable, reproducible results. These CGMP requirements will help to achieve these results.

The dietary supplement CGMP requirements are also reasonable when viewed in the context of the act as a whole. *See Brown & Williamson*, 529 U.S. at 133. Our mission is, in part, to protect the public health by ensuring that foods are safe, wholesome, sanitary, and properly labeled (section 903(b)(2)(A) of the act) (21 U.S.C. 393(b)(2)(A))). Section 701(a) of the act (21 U.S.C 371(a)) gives us the authority to promulgate regulations for the efficient enforcement of the act in order to “effectuate a congressional objective expressed elsewhere in the Act” (*Association of American, Physicians and Surgeons, Inc. v. FDA*, 226 F. Supp. 2d 204 (D.D.C. 2002) (citing *Pharm. Mfrs. Ass’n. v. FDA*, 484 F. Supp. 1179, 1183 (D. Del. 1980))). The final rule is designed to help ensure that dietary supplements consistently are manufactured to produce the product established by the manufacturer, to bear the label identified in the master manufacturing record, and to prevent

adulteration. The requirements are written to facilitate efficient and effective action to enforce their terms when necessary.

Some provisions of the dietary supplement CGMP final rule may be similar to the existing drug CGMP regulations. However, we have not modeled these regulations after the drug CGMP regulations. Controls that relate to certain product forms (e.g., tablets, capsules, powder, softgel) are required in this final rule based on the specific characteristics of dietary supplements and the hazards associated with these forms, not, as some comments imply, based on a desire to emulate drug CGMP requirements. The act does not state that there may not be similarities between the dietary supplement CGMP requirements and the CGMP requirements for drugs or other non-food products. Inasmuch as food CGMP regulations and other CGMP regulations are all based on CGMP principles, it is neither surprising nor impermissible that there are similarities between the dietary supplement CGMP requirements and drug or device CGMP requirements. Although we do not agree that any of the CGMP requirements exceed drug GCMP requirements, even if a particular requirement did, it is not prohibited under the statute. As long as the CGMP final rule is “modeled after” the food CGMP regulations, we have satisfied the statutory requirements. As noted, our interpretation of “modeled after” means that the dietary supplement CGMP final rule provisions share similar objectives and/or use similar means as the existing food CGMP regulations. To the extent that there are similarities to drug CGMP regulations, those similarities are appropriate and not prohibited by section 402(g) of the act.

Consistent with our role “to fill in, through interpretation, matters of detail related to [the statute’s] administration,” *Barnhart v. Walton*, 535 U.S. 212, 225 (2002), we applied our scientific expertise, policy judgment, and

experience to promulgate dietary supplement CGMP requirements that will protect the public health and effectively implement our statutory authority to prescribe dietary supplement CGMP. See *United States v. Mead*, 533 U.S. 218, 227–228 (2001); *Nationsbank of North Carolina v. Variable Annuity Life Ins. Co.*, 513 U.S. 251, 256–58 (1995); *Chevron*, 467 U.S. at 844; *Forester v. Consumer Product Safety Com.*, 559 F.2d 774, 783 (D.C. Cir. 1977).

B. Records Authority

(Comment 19) Some comments state that requirements related to record keeping and access to such records are necessary to allow our inspectors to assess the adequacy of a dietary supplement manufacturer's practices. Additional comments state that access to records is necessary to ensure that CGMP requirements are followed and to protect the public health. Several comments identify specific types of records we should require in a final rule, including written procedures, batch and master manufacturing records, distribution records, and lot numbers. Another comment states that training records should be required because the qualifications and training of employees affects product quality.

Other comments, however, state that the record retention and access requirements seem to be modeled after drug CGMP and not food CGMP. Other comments state that, even though records may be necessary to ensure that CGMP requirements are followed, we do not have authority to require access to and copying of such records. Some comments assert the authority to establish regulations for dietary supplement CGMP does not imply there is authority to inspect records. Several comments state we cannot rely on section 701 of the act because there is not another section of the act that authorizes us access to company records for dietary supplement CGMP and section 701(a)

of the act does not itself give us the authority we need to require records inspection. Another comment suggests that the absence of an express grant of records inspection authority means that records inspection is not necessary for the efficient enforcement of the act.

Some comments assert that we have no record inspection authority under section 704(a) of the act (21 U.S.C 374(a)). A few comments suggest that, because records inspection authority was not expressly granted in DSHEA's statutory language, as it was for OTC drugs and medical devices, Congress provided no authority for records inspection for dietary supplement CGMP. The comments state that we have a longstanding interpretation that section 704 of the act does not give us access to a food manufacturer's records. Several comments state that it was sufficient to have voluntary records access, stating that many companies are willing to provide access to records.

Other comments say that our record inspection authority for dietary supplement CGMP is limited to that under section 306(a) of the Public Health Security and Bioterrorism Preparedness and Response Act of 2002 (Bioterrorism Act) (21 U.S.C. 350(c)), i.e., when we have a "reasonable belief that an article of food is adulterated and presents a threat of serious adverse health consequences * * *" Another comment suggests an alternative standard to that in section 306(a) of the Bioterrorism Act of a "reasonable belief that there is a public health hazard" for when we may access records.

One comment cites *In the Matter of Establishment Inspection of Medtronic, Inc.*, 500 F. Supp 536 (D. Minn. 1980), to support its assertion that we exceeded our statutory inspection authority in the dietary supplement CGMP record requirements. One comment states that a warrantless inspection of dietary supplement CGMP records and criminal consequences that may be imposed

under the act for failure to comply with the act provide a “powerful argument against expanding the Agency’s inspection authority any further” and raise “serious constitutional concerns.” Several comments ask us to clarify our jurisdiction for records inspection requirements or delete proposed § 111.125(c).

Still other comments seek confirmation that the confidential and trade secret information obtained by us under the rule would be protected from disclosure under applicable statutes. Among other things, the comments cite the Trade Secrets Act, 18 U.S.C. 1905, and the Freedom of Information Act (FOIA), 5 U.S.C. 552(b)(4). Some comments express concern that records inspection would violate “rights to privacy of corporate manpower” or would compromise trade secrets. The comments request the rule specifically reconfirm our obligations under these laws.

(Response) We disagree with the comments suggesting that we have no authority to require dietary supplement manufacturers to maintain records to comply with CGMP under section 402(g) of the act; that the absence of an express grant of records authority means records are not needed for the efficient enforcement of the act; and that Congress meant, by its silence, that we have no authority to issue records requirements. Clearly, just as Congress is not expected to express “every single evil sought to be corrected” in a grant of authority to promulgate a rule, it can not be expected to articulate every requirement that is within an agency’s delegated authority (*American Trucking Assoc. v. United States*, 344 U.S. 298, 309–10 (1953)).

Agencies are expected to bring their expertise to bear on what requirements are necessary that will not “directly frustrate the success of the regulation undertaken by Congress” (id. at 311). In this instance, Congress has

not expressed any specific intent regarding recordkeeping for dietary supplements but has directed FDA to use other food CGMP regulations, which require recordkeeping and FDA access to records, as models for these regulations. Congress has delegated substantial and sufficiently specific authority to us to promulgate recordkeeping and access regulations (*Cf. United States v. Storer Broadcasting*, 351 U.S. 192, 202-03 (1956) (upholding a rule that established limitations on broadcast licensing that were “not specifically authorized by statute”)). As stated earlier in this section, the “modeled after” language in section 402(g) of the act is ambiguous with respect to what specific CGMP requirements we are to include in this final rule. At the time Congress enacted section 402(g) of the act there were several food regulations that contained recordkeeping and record access requirements. We included records requirements in the food CGMP regulations for infant formula (part 106), low acid food (part 113), acidified food (part 114), and bottled water (part 129). Accordingly, the directive in section 402(g) of the act is sufficient authority for our recordkeeping requirements in this final rule. In addition, our authority to establish records requirements has been upheld under other provisions of the act, which lacked explicit recordkeeping authority for FDA, where we have found records to be necessary (*National Confectioners Assoc. v. Califano*, 569 F.2d 690, 693-94 (D.C. Cir. 1978) (upholding requirements for source coding and distribution records based on the statutory scheme as a whole)).

Moreover, records are an indispensable component of CGMP. The records required by this final rule provide the foundation for the planning, control, and improvement processes that constitute a quality control system. Implementation of these processes in a manufacturing operation serves as the backbone to CGMP. The records will show what is to be manufactured; what

was, in fact, manufactured; and whether the controls that the manufacturer put in place to control the identity, purity, strength, and composition and limits on contaminants and to prevent adulteration were effective. Further, records will show whether and what deviations from control processes occurred, facilitate evaluation and corrective action concerning these deviations (including, where necessary, whether associated batches of product should be recalled from the marketplace), and enable a manufacturer to assure that the corrective action was effective. Written procedures also will help ensure that personnel follow hygienic practices; permit evaluation of whether equipment, including software that may run the equipment, performs as it is intended; and help ensure that the equipment is properly maintained and adequately cleaned.

The CGMP final rule establishes the parameters for the production and process control system in which dietary supplements are to be manufactured. The dietary supplement manufacturer establishes the identity, strength, purity, and composition of the supplement it manufactures (final § 111.70); determines whether the established specifications are met (final § 111.73); uses the tests it needs to ensure that those characteristics are consistently met (final §§ 111.75 and 111.315); and identifies the steps necessary to ensure that any necessary tests or examinations are completed, reviewed, and recorded in a timely fashion before the dietary supplement is released for distribution to the public (final §§ 111.110 and 111.325(b)(2)). The CGMP final rule also requires that the manufacturer establish written procedures for its quality control operations to ensure the personnel performing this function provide proper review and oversight of the production and process control system, have the knowledge and experience to identify and anticipate possible problems in the

manufacturing of the dietary supplement, and ensure corrective measures are taken promptly when problems occur (final §§ 111.103 through 111.140). The final rule also requires that the manufacturer establish the “master recipe(s)” for the dietary supplement(s) it manufactures so that such recipe(s) can be followed for each batch produced (final §§ 111.205 through 111.210). In sum, manufacturers cannot operate without records because critical elements in a manufacturing process are entirely dependent on information written or captured in the form of a record.⁶ Such records are also necessary to protect consumers by enabling manufacturers to identify and recall problematic products as necessary and make necessary corrections to deviations in their processes.

The authority granted us under sections 402(g) and 701(a) of the act not only includes the authority to establish record requirements, but also includes access to such records. Without such authority, the dietary supplement CGMP requirements are, practically speaking, not enforceable. Under section 402(g)(1) of the act, the failure to meet any CGMP requirements, including the failure to have a record that is required by this final rule, renders a dietary supplement so manufactured to be adulterated as a matter of law. The introduction or delivery for introduction into interstate commerce of an adulterated dietary supplement is a prohibited act under section 301(a) of the act (21 U.S.C. 331(a)), and acts done to an ingredient in a dietary supplement, or to a dietary supplement, while held for sale after shipment in interstate commerce that result in the ingredient or dietary supplement being adulterated violates section 301(k) of the act (21 U.S.C. 331(k)). Thus, in order for us to determine whether the dietary supplement product is adulterated and whether a

⁶It is also worth noting that standard references used in many industries establish clear expectations for documentation and recordkeeping practices for assuring quality control in manufacturing operations (Refs. 9 and 13).

manufacturer has committed a prohibited act, we must have access to the manufacturer's records that we are requiring to be kept under section 402(g) of the act.

In light of the foregoing, without access to such records, we would not know whether a manufacturer was complying with the procedures and processes required in this final rule. For example, our investigator must have access to the test results for the identity of a dietary ingredient to determine whether such ingredient meets the manufacturer's specification for identity. The investigator needs to understand, by reviewing a record, what the software that runs a production operation is set up to do and whether it performs those functions to achieve the desired product characteristics. Observation of these processes alone, by an investigator, would not allow that investigator to evaluate compliance with this final rule. Moreover, records often cannot be thoroughly evaluated by the investigator on site. In such cases, records must be readily available to food experts at the Center for Food Safety and Applied Nutrition (CFSAN) and agency consultants. We must have accurate, reliable, and objective data about the manufacturing specifications to be able to achieve an enforceable rule.

We also disagree with comments stating our records inspection authority is limited to that provided by section 306(a) of the Bioterrorism Act. There is no basis to conclude that Congress intended to limit our authority to inspect records, to enforce section 402(g) of the act, to the records inspection authority under the Bioterrorism Act. The Bioterrorism Act, enacted almost 8 years after section 402(g), to address credible threats of serious adverse health consequences or death to humans and animals, required recordkeeping to

identify the immediate previous sources and the immediate subsequent recipients of food (21 U.S.C. 350c).

There is nothing in the Bioterrorism Act that reflects any Congressional intent to modify section 402(g) of the act. In fact, section 414(d)(1) of the act (21 U.S.C. 350c(d)(1)), added by section 306(a) of the Bioterrorism Act, shows a contrary intent. Section 414(d)(1) provides that “This section shall not be construed—(1) to limit the authority of the Secretary to inspect records or to require establishment and maintenance of records under any other provision of this Act.” Moreover, Congress, in the legislative history to the Bioterrorism Act, supported our general approach of requiring recordkeeping pursuant to authority in section 701(a) of the act in combination with other provisions.⁷ We are not relying on section 704 of the act for its underlying authority to require recordkeeping and records access in this final rule. Those comments asserting that we do not have such authority and the underlying references, for example, to past hearings on records inspection authority under section 704 of the act, are not controlling with regard to the action we are taking under sections 402(g) and 701(a) of the act. When there are other bases for jurisdiction and tools to protect the public interest, we may use what “will be the most effective in advancing the Congressional objective” (*U.S. v. Midwest Video Corp.*, 406 U.S. 649, 656 (1972)).

Some comments stated that our access to dietary supplement records is not consistent with constitutional jurisprudence. We disagree. The comment

⁷In discussing section 306 of the Bioterrorism Act (Maintenance and Inspection of Records for Foods), Congress stated, “The managers did not adopt a Senate proposal to authorize the Secretary to require the maintenance and retention of other records for inspection relating to food safety, because the Secretary has authority under section 701(a) of the [act] to issue regulations for the ‘efficient enforcement of this Act’ and this authority, in combination with other provisions (such as section 402 [of the act]), gives the Secretary the authority to require appropriate record keeping in food safety regulations.” (H.R. Conf. Rep. No. 107-481, at 135 (2002), (Ref. 14)).

which expressed concern about “constitutional issues” in the context of an FDA inspection of records during a warrantless FDA inspection expressed concern about the criminal liability that could be imposed on a manufacturer under the act (citing *United States v. Dotterweich*, 320 U.S. 277 (1944) and *United States v. Park*, 421 U.S. 658 (1975)). To the extent that the comment asserts that the records access established in this final rule constitutes an improper search and seizure under the Fourth Amendment, we disagree.

The dietary supplement industry, as the food industry as a whole, is a pervasively regulated industry that is subject to warrantless inspections (*see, e.g., United States v. Biswell*, 406 U.S. 311, 315 (1972) (“In the context of a regulatory inspection system of business premises * * * the legality of the search depends not on consent but on the authority of a valid statute.”); *United States v. New England Grocers Supply Co.*, 488 F. Supp. 230, 238 (D. Mass. 1980) (holding that a warrantless inspection under 21 U.S.C. 374 is “fully consistent with the Fourth Amendment”); *United States v. Acri Wholesale Grocery Co.*, 409 F. Supp. 529, 533 (S.D. Iowa 1976) (holding that a warrantless inspection, which includes photographic activities, conducted under 21 U.S.C. 374 does not violate the Fourth Amendment); *United States v. Business Builders, Inc.*, 354 F. Supp. 141, 143 (N.D. Okla. 1973) (“the statute takes the place of a valid search warrant”); *United States v. Del Campo Baking Mfg. Co.*, 345 F. Supp. 1371 (D. Del 1972) (finding warrantless inspection of food establishment lawful under 21 U.S.C. 374)).

As explained earlier in this section, we have ample authority, under sections 402(g) and 701(a) of the act, to require that certain records be kept and accessible to us upon inspection. Records access is imperative to the efficient enforcement of the dietary supplement CGMP final rule, and we are

not prohibited from requiring access to these records under sections 402(g) and 701(a) of the act (See *Permian Basin Area Rate Cases*, 390 U.S. 747, 780 (1968) (“in the absence of compelling evidence that such was Congress’ intention * * * [the court should not] prohibit administrative action imperative for the achievement of an agency’s ultimate purposes.”)).

We also disagree with the comment suggesting that voluntary records access is sufficient. In our experience, many manufacturers are not willing, as the comments suggest, to provide records voluntarily to us (Ref. 15). Moreover, it is often the case that the most uncooperative manufacturers are the very ones whose records and processes are deficient. Without mandatory requirements for agency access to records required by the final rule, we could not enforce and there would be minimal incentives for manufacturers to comply with the rule, which would frustrate Congressional intent in enacting section 402(g) of the act.

We also disagree with the comment that cited *In the Matter of Establishment Inspection of Medtronic, Inc.*, 500 F. Supp. 536 (D. Minn. 1980), to suggest that our proposed recordkeeping requirements exceed our statutory inspection authority. As already discussed, we are not relying on section 704 of the act for our authority to require access to dietary supplement CGMP records. Thus, to the extent the comment cited to *Medtronic* as an example of the statutory authority for inspection of device records under section 704 of the act, *Medtronic* is not pertinent to our authority for records access in this final rule.

Finally, we disagree that the records access in this final rule will violate any protection a manufacturer has with respect to protection of confidential commercial or financial information or trade secrets. Trade secrets and

commercial or financial information that is privileged or confidential are protected from disclosure under FOIA and other laws (see, e.g., 21 U.S.C. 331(j), 18 U.S.C. 1905). Further, our FOIA regulations set forth the specific procedures for assuring such protection.

It was not clear from the comments what was meant by “rights to privacy of corporate manpower.” We note that §§ 20.63 and 20.64 contain provisions for the protection of personal privacy.

C. Public Health Service Act Authority

(Comment 20) One comment acknowledges that we have authority under the PHS Act to regulate intrastate activities that may cause the spread of communicable diseases. The comment states that, in any situation in which we need to exercise our authority over any disease-causing substance within the State where a component or dietary supplement is manufactured, packed, or held, we can and should exercise our authority under the PHS Act. However, the comment asserts that nothing in the preamble clearly states whether we believe that the final rule will be, in its entirety, binding on manufacturers, packers, and holders of dietary supplements who are engaged solely in intrastate commerce, and that we have not requested comment on this specific issue. The comment requests that we clearly state that the final rule applies only to interstate commerce, except for activities that may spread communicable diseases.

(Response) We address each of these issues in turn.

1. The Communicable Disease Risk Posed by Dietary Supplements

There are communicable disease risks related to the manufacture of dietary supplements that are appropriately addressed not only under the act, but, as the comment acknowledges, also under the PHS Act. Microorganisms,

including *Salmonella enterica* (Salmonella), *Campylobacter jejuni*, and enterohemorrhagic *Escherichia coli* 0157:H7 (EHEC), are well-known causes of communicable diseases, and may be present in dietary supplements and their components. There are a number of microorganisms that cause communicable diseases and that may be found in components or dietary supplements. These microorganisms cause serious effects and symptoms. For example, Salmonella causes salmonellosis, which affects the gastrointestinal (GI) tract and is characterized by diarrhea, fever, abdominal cramps, headache, nausea, and vomiting (Ref. 16). In a small portion of healthy people (1 to 4 percent), infection spreads from the GI tract into the blood stream, which can be life-threatening. Persons with immune compromising conditions (such as cancer, Acquired Immunodeficiency Syndrome (AIDS), autoimmune disorders) are at greater risk of blood stream infection (Ref. 16).

Campylobacteriosis, often due to infection with *Campylobacter jejuni*, is characterized by diarrhea, fever, and abdominal cramps, which can be severe (Ref. 17). These symptoms frequently relapse, and the disease may become chronic in immune compromised persons. People with campylobacteriosis are also at increased risk of developing certain post-infectious complications, which will prolong their recovery.

EHEC may cause infections with a very low infectious dose (as low as 2 to 45 organisms), and may result in non-bloody and bloody diarrhea, hemolytic-uremic syndrome (a cause of red blood cell destruction, damage of blood vessel walls, and, in severe cases, kidney failure (especially in young children)), thrombotic thrombocytopenic purpura (i.e., a blood disorder characterized by low platelets, low red blood cell count, abnormalities in

kidney function, and neurological abnormalities (especially in adults)), and death (Ref. 18).

Animal tissues (e.g., organs from livestock), as well as botanicals, used as components in dietary supplements may contain EHEC, Salmonella, and *Campylobacter jejuni*. In addition, because the same microorganisms are also present in the environment, they may contaminate components during manufacturing activities. Moreover, people who harbor those pathogens could transmit them to components and dietary supplements during processing. Therefore, components and dietary supplements, as potential sources of communicable diseases, may be regulated under the PHS Act.

For these microorganisms (e.g., EHEC, Salmonella, and *Campylobacter jejuni*) humans carry and transmit infections through their feces or by direct contact with other persons. For other microorganisms, domestic and wild animals serve as the reservoir, and humans become infected when contaminated tissues of infected animals are used in dietary supplements. For both categories of microorganisms, dietary supplements can also become contaminated indirectly by human and animal fecal contamination of water or through the production or processing environment.

Dietary supplements may contain a variety of components derived from domestic and wild animals, such as powders prepared from whole or partial gecko, deer antler velvet, and organs, such as cow liver and brain, pork stomach, or sheep spleen from common domestic livestock. Each of these tissues may be contaminated with microorganisms such as Salmonella, *Campylobacter jejuni*, and EHEC. Even clinically normal animals obtained from safe sources may harbor these communicable pathogens and result in contaminated products (Ref. 19). (Information on these animals and potential

pathogens can be accessed at <http://www.fsis.usda.gov/Science/Microbiology/index.asp>). Dietary supplements also may contain crustacean or molluscan shellfish or components prepared from them, such as glucosamine from shrimp exoskeletons and oyster extract, that may be contaminated with *Vibrio* species, including *V. parahaemolyticus*. *Vibrio* species are natural inhabitants of shellfish harvest waters, and shellfish are commonly naturally contaminated, especially during times of the year when harvest waters are warm (Refs. 20 through 23). *V. parahaemolyticus* most often causes gastroenteritis characterized by diarrhea, abdominal cramps, nausea, vomiting, and fever (Ref. 24).

Dietary supplements may also contain botanicals (plants) that may harbor microorganisms, including organisms from animal feces (*Salmonella* and *Shigella* spp., *Escherichia coli*), and organisms arising from handling (*Staphylococcus aureus*), harvesting, processing, and transportation.

Components contaminated with microorganisms must be treated to prevent the finished dietary supplements from being contaminated. The processes used to manufacture dietary supplements do not, by themselves, always eliminate the microorganisms. Studies show, for example, that microorganisms, such as EHEC and *Salmonella*, can even survive the tablet production process and thereby expose consumers (Ref. 25).

The industry is aware of the dangers of using components contaminated with *Salmonella* and other microorganisms. For example, in 2001, a component manufacturer recalled 2,400 pounds of pepsin contaminated with *Salmonella*. As a result, a number of dietary supplement manufacturers issued recalls for their dietary supplements that contained the pepsin. In the press releases accompanying the recalls, the dietary supplement manufacturers

warned consumers of the possible dangers of Salmonella contamination, and encouraged consumers to either destroy or return the supplements (Ref. 26).

Therefore, because of the communicable disease concerns associated with dietary supplements, we are asserting legal authority under the PHS Act in support of the final rule. As discussed in the following section of this document, our authority under the PHS Act is not limited to interstate activities. It also covers intrastate activities.

2. Activities For Which We Are Asserting Legal Authority Under the PHS Act

There are many opportunities for components and dietary supplements to become contaminated with microorganisms that spread communicable diseases. The final rule requires firms to take all the necessary precautions during the manufacture of a dietary supplement to prevent such contamination.

These precautions, for example, include: Performing manufacturing operations under conditions and controls that protect against potential microorganism growth; washing or cleaning components that contain soil or other contaminants; performing microbiological testing, as necessary, to prevent the use of contaminated components; sterilization, pasteurization, freezing, refrigeration, and controlling pH, humidity, and water activity (a_w), or using other effective means to remove, destroy, or prevent the growth of microorganisms and decomposition; and holding components and dietary supplements that can support the growth of infectious microorganisms of public health significance in a manner that prevents them from becoming adulterated.

Failure to properly clean components, or take any other appropriate steps, such as those listed in the previous paragraph, could lead to pathogen growth

and the spread of communicable diseases. If, for example, a dietary supplement manufacturer purchased an animal-derived ingredient that harbored *Salmonella enterica*, but failed to take the steps necessary to inactivate the pathogen, the consumption of the dietary supplement could lead to the spread of salmonellosis.

The final rule also requires firms to take measures to exclude from certain operations any sick persons who might contaminate material, including components, dietary supplements, and contact surfaces used to manufacture, package, label, or hold a dietary supplement.

D. The Interstate Commerce Nexus for the Final Rule

1. The PHS Act

(Comment 21) Several comments assert that, although the PHS Act may extend to some intrastate activities, its reach is very limited. The comments appear to conclude that the reach of the PHS Act and the act extends only to situations in which the finished dietary supplement is shipped in interstate commerce.

(Response) We do not agree that this view is correct. The PHS Act extends to intrastate commerce. Under section 361 of the PHS Act (42 U.S.C. 264), we may “make and enforce such regulations as in [our] judgment are necessary to prevent the introduction, transmission, or spread of communicable diseases from foreign countries into the States or possessions, or from one State or possession into any other State or possession.”

In *Louisiana v. Mathews*, 427 F. Supp. 174, 176 (E.D. La. 1977), the court upheld FDA’s regulation that banned the sale of small turtles to prevent the spread of disease caused by turtles harboring *Salmonella* and *Arizona* microorganisms. The ban covered both interstate and intrastate sales. The court

held that the intrastate ban is not only authorized by the law, but, under modern conditions of transportation and commerce “is clearly reasonable to prevent the interstate spread of disease” (id.).

We are authorized under the PHS Act to regulate conduct that occurs within a State to the extent necessary to prevent the interstate spread of communicable diseases. Such is the present case with respect to the provisions of the dietary supplement CGMP final rule for which section 361 of the PHS Act provides authority.

2. The Act

The act extends to the sale of a dietary supplement that was manufactured and distributed entirely in one State, if the supplement contains any ingredient or uses any component that came from outside of that State. Such a dietary supplement is subject to section 301(k) of the act, which prohibits “[t]he alteration, mutilation, destruction, obliteration, or removal of the whole or any part of the labeling of, *or the doing of any other act with respect to, a food, drug, device, or cosmetic, if such act is done while such article is held for sale (whether or not the first sale) after shipment in interstate commerce and results in such article being adulterated or misbranded.*” (emphasis added). See also 21 U.S.C. 321(b)(3) (defining food to include articles used as components of food).

The interstate commerce prerequisite under section 301(k) or section 304(a) (21 U.S.C. 334(a)) of the act is established when one or more components used in the manufacture of the product have crossed State lines. This principle is known as “component jurisdiction” (See, e.g., *Baker v. United States*, 932 F.2d 813, 814–15 (9th Cir. 1991); *United States v. Article of Food* * * * *Coco Rico, Inc.*, 752 F.2d 11, 14 (1st Cir. 1985); *United States v. Dianovin*

Pharmaceuticals, Inc., 475 F.2d 100, 103 (1st Cir.), cert. denied, 414 U.S. 830 (1973) (“appellants’ use of components shipped in interstate commerce to make vitamin K for injection brought their activities within § 331(k)”); *United States v. Cassaro, Inc.*, 443 F.2d 153, 155–56 (1st Cir. 1971); *United States v. Detroit Vital Foods, Inc.*, 330 F.2d 78, 81–82 (6th Cir.), cert. denied, 379 U.S. 832 (1964); *United States v. Allbrook Freezing & Cold Storage, Inc.*, 194 F.2d 937, 939 (5th Cir. 1952); *United States v. Varela-Cruz*, 66 F.Supp.2d 274, 277–281 (D. P.R. 1999)).

Nor does it matter that the interstate product component comprises only a minute part of the article, *United States v. Miami Serpentarium Laboratories*, [1981—1982 Transfer Binder] Food Drug Cosm. L.Rep. (CCH) paragraph 38,164 at 38,930 (S.D. Fla. 1982); *United States v. 14 Cases * * * Narengo*, 374 F.Supp. 922, 925 (W.D. Mo. 1974), or if the interstate ingredient combines with others to form a different product. *Detroit Vital Foods*, 330 F.2d at 81; *United States v. 40 Cases * * * Pinocchio Brand * * * Oil*, 289 F.2d 343, 346 (2d Cir.), cert. denied, 368 U.S. 831 (1961).

Finally, we note that section 709 of the act creates a presumption of interstate commerce (see 21 U.S.C. 379a (“In any action to enforce the requirements of this Act respecting a device, food, drug, or cosmetic the connection with interstate commerce required for jurisdiction in such action shall be presumed to exist.”))).

In conclusion, the final rule covers not only finished products that have moved in interstate commerce but also products made from ingredients or components that have moved in interstate commerce. This is true regardless of the amount of the ingredient or component in the product and regardless of whether the finished dietary supplement has itself moved in interstate

commerce. The final rule also covers products, components, and ingredients that may contribute to the spread of communicable disease, regardless of whether the component, ingredient, or product has itself moved in interstate commerce.

3. Commerce Clause

(Comment 22) One comment states that we must be “mindful of the limits” imposed on the regulation of intrastate commerce by the Supreme Court in *United States v. Lopez*, 514 U.S. 549 (1995). The comment asserts that we may only regulate intrastate activity that has a “substantial effect” on interstate commerce and activity that “exerts a substantial economic effect on interstate commerce.”

(Response) The final rule is consistent with the *Lopez* decision. Among the cases cited by the Court in *Lopez* as support for its decision is *Wickard v. Filburn*, 317 U.S. 111 (1942), which involved the production and consumption of homegrown wheat. In that case, the Court explained: “although Filburn’s own contribution to the demand for wheat may have been trivial by itself, that was not enough to remove him from the scope of federal regulation where, as here, his contribution, taken together with that of many others similarly situated, is far from trivial” (*Lopez*, 514 U.S. at 556). The same is true for dietary supplement manufacturers. Therefore, the requirements of the final rule are consistent with the Commerce Clause of the Constitution.

E. Fifth Amendment

(Comment 23) Several comments allege a number of the sections of the proposed regulation are unconstitutionally vague and violate the Administrative Procedure Act (APA) because the rule would be “contrary to constitutional right, power, privilege, or immunity.” The comments express

concern that if such terms are not defined or deleted, there would be no fair notice on what conduct is prohibited and would result in “unbridled discretion” in how the rule will be enforced. The comments focus on provisions containing words such as “adequate,” “qualified,” “readily accessible,” “convenient,” “suitable,” “appropriate,” and “necessary.” For example, one comment notes that proposed § 111.15(e) would require physical plant plumbing to be of an adequate size and design and to be adequately installed and maintained. The comment objects to the section on the ground that “what constitutes ‘adequate’ in those contexts is left undefined.”

(Response) We disagree these terms are vague or that the identified terms should be deleted from the final rule. The qualifying terms objected to in the comments have been in use since the umbrella food CGMP rule (part 110) was first promulgated in 1969. For example, this regulation included requirements that: “[p]lant buildings and structures shall be suitable in size;” there must be “sufficient space” for equipment and storage materials; there must be “adequate lighting;” and protection against pests must be provided “where necessary” (see 34 FR 6977 at 6978, April 26, 1969). The court in *National Association of Pharmaceutical Manufacturers. v. Department of Health & Human Services*, 586 F.Supp. 704 (S.D.N.Y 1986), addressed the very question of whether terms such as “adequate,” “appropriate,” “proper,” “sufficient,” and “suitable,” in the drug CGMP regulation were vague. The court found that the drug CGMP regulation containing such terms was “sufficiently definite to give notice of the required conduct to one who would avoid [their] penalties, and to guide the judge in [their] application * * *” (Id. at 753). The court so held, in part, in light of the fact that the drug CGMP statute was upheld against a constitutional vagueness attack in *United States v. Bel-Mar*

Laboratories, Inc., 284 F. Supp. 875, 883 (E.D.N.Y. 1968) (“the phrase ‘current good manufacturing practice’ is not strange to those in the trade to whom the subject section is directed.”). Furthermore, the use of such “ordinary terms to express ideas which find adequate interpretation in common usage and understanding” are not the types of terms that have been held to be unconstitutionally vague (*Boyce Motor Lines v. United States*, 342 U.S. 337, 342 (1952)). Some of these very terms have been in use for over 30 years in food CGMP regulations.

No comments were submitted objecting to the use of such terms, when the umbrella food CGMP rule was revised in 1986 (see 51 FR 22458, June 19, 1986). Also, when we began work on the dietary supplement CGMP rule, we received and published for comment an industry draft of a CGMP regulation for dietary supplements. The industry draft used many of the same terms. For example, it provides in part: “Plumbing shall be of adequate size and design and adequately installed and maintained” (62 FR 5700 at 5703, February 6, 1997). Thus, there has been sufficient common usage of these terms in the food industry and, in particular, the dietary supplement industry to enable manufacturers, and those who enforce the requirements, to comprehend and apply such terms “with a reasonable degree of certainty” to their particular operations (*Boyce Motor Lines v. United States*, 342 U.S. at 340 (“[F]ew words possess the precision of mathematical symbols, most statutes must deal with untold and unforeseen variations in factual situations, and the practical necessities of discharging the business of government inevitably limit the specificity with which legislators can spell out prohibitions [and therefore] no more than a reasonable degree of certainty can be demanded.”)). The same reasoning applies here. It addresses “untold and unforeseen variations in

factual situations” and, as such, “no more than a reasonable degree of certainty can be demanded.”

Agencies are permitted to, and indeed must, use such qualifying terms to address the variety of conditions that exist at different companies. We do not need to, nor could we, predict with mathematical precision how many inches or feet, for example, would be “adequate space” to allow for cleaning a particular piece of equipment that could be applied to every size of facility and every operation (*id.*). Moreover, defining such terms too precisely would unduly restrict the application of the regulation to a very narrow, limited set of circumstances and not provide industry with the needed flexibility to address the number and variety of types of manufacturing operations that Congress intended for this rule to cover (see *Freeman United Coal Mining Company v. Federal Mine Safety and Health Review Commission*, 108 F.3d 358, 363 (D.C. Cir. 1997) (citations omitted) (upholding a regulation that required equipment to be “maintained in good repair,” the court rejected the vagueness challenge: “specific regulations cannot begin to cover all of the infinite variety of [conditions at firms and that] * * * [b]y requiring regulations to be too specific [courts] would be opening up large loopholes allowing conduct which should be regulated to escape regulation.”); *United States v. Bel-Mar Laboratories, Inc.*, 284 F. Supp. at 883 (rejecting a vagueness challenge to the CGMP requirements for drugs, noting that “[a]s a matter of fact, there are responsible segments of opinion within the industry itself which oppose a greater degree of specificity in this area.”).

Finally, it is important to understand that rules are not unconstitutionally vague simply because they require interpretation by regulated persons. For example, courts have held that the term “insanitary conditions” in the act is

not unconstitutionally vague (See *Golden Grain Macaroni Co. v. United States*, 209 F.2d 166, 168 (9th Cir. 1953) (citing *Boyce Motor Lines*, supra); *Berger v. United States*, 200 F.2d 818 (8th Cir. 1952)). In *Berger*, the court rejected the claim that the term “insanitary condition” is unconstitutionally vague on the ground that it does not specify the “degree of insanitation” required for a violation (*id.* at 822). A law may require a person to make “estimates of the degree of dirtiness and lack of sanitation” which may result in a violation (*id.*, see also *Boyce Motor Lines v. United States*, 342 U.S. at 340 (It is not “unfair to require that one who deliberately goes close to an area of proscribed conduct shall take the risk that he may cross the line”)). There are sufficient protections under the act to overcome any concerns related to how it will be criminally enforced. We disagree that such terms will lead to “unbridled discretion” on how the rule is enforced.

In short, we find that the rule is not unconstitutionally vague, and does not violate section 706(2)(B) of the APA (5 U.S.C. 706(2)(B)).

F. Miscellaneous

(Comment 24) One comment states that the proposed rule violates section 402(f)(1)(A)(i) and (f)(1)(A)(ii) of the act (21 U.S.C. 342 (f)(1)(A)(i) and (f)(1)(A)(ii)), which deems a dietary supplement adulterated if it contains a dietary ingredient that presents an unreasonable risk of illness or injury under conditions of use in labeling or ordinary conditions of use, if none are suggested or recommended in labeling. Under section 402(f) of the act, the Government bears the burden of proof to show that a dietary supplement is adulterated. The comment states that the proposed rule reversed the presumption under section 402(f) of the act, and would revise the rule to require us to first show a violation under section 402(f) of the act before we

could take any enforcement action under section 402(g). Another comment states that, because the rule was intended to enable manufacturers to be able to detect and avoid adulteration through CGMP, the proposed rule created a presumption that dietary supplements are adulterated until proven otherwise.

(Response) The final rule does not violate section 402(f) of the act. Section 402(f) and (g) of the act provide two independent bases under which we may take enforcement action against dietary supplements. A dietary supplement may be adulterated either because a manufacturer has failed to follow a CGMP requirement, or because a dietary supplement presents an unreasonable risk of illness or injury, or both. There would be no reason to assert a second basis for adulteration under section 402(g) of the act if one always had to demonstrate adulteration under section 402(f) of the act as a prerequisite.

We also disagree with the comment that the proposed rule creates a presumption that the dietary supplement is adulterated simply because the proposed requirements would enable a manufacturer to detect and avoid adulteration. The requirements for CGMP are prophylactic and are designed in part to ensure that all aspects of manufacturing, from receipt through distribution, provide the necessary controls and monitoring to ensure the quality of the dietary supplement, including that it is manufactured, packaged, labeled, and held in a manner to prevent adulteration.

(Comment 25) One comment states that, if there is reduced competition through the enforcement of the rule, there will be a secondary effect of elimination of speech on dietary supplement innovative uses.

(Response) The comment seems to conclude that, if a dietary supplement manufacturer is not able to stay in business due to adverse enforcement actions against it by us, or elects to not go into business based on the possibility of

enforcement action by us, there will be reduced competition due to fewer products, less labeling, and “elimination of speech on innovative uses.” To the extent that the comment is suggesting that the dietary supplement CGMP requirements are unconstitutionally overbroad, this argument is wholly without merit (*Cf. Wisconsin v. Mitchell*, 508 U.S. 476, 488–89 (1993) (finding no merit to an overbreadth argument that the possibility of enhanced sentences based on prior racially motivated speech or associations constitutes an impermissible chill on free speech)). Manufacturing a dietary supplement in a manner that violates the CGMP requirements causes the product to be adulterated, and therefore, unlawful. The fact that a manufacturer may not stay in business, or elects not to enter business, due to: (1) Our implementation of CGMP requirements or (2) our enforcement against a product that violates CGMP requirements, does not mean that we are somehow prohibiting speech. In any event, there is no First Amendment protection for speech that concerns unlawful activity under the first prong of the test set out in *Central Hudson Gas & Electric Corp. v. Public Service Commission*, 447 U.S. 557 (1980). Therefore, the comment’s suggestion that there is elimination of speech based on the rulemaking is not supportable. The requirements in the final rule do not infringe on a manufacturer’s right to lawfully label and market a dietary supplement.

VI. What Comments Did We Receive on the General Provisions? (Subpart A)

A. Organization of Final Subpart A

Proposed subpart A contained five provisions regarding the scope of the proposed rule, definitions, and exclusions. Table 2 of this document lists the sections in final subpart A and identifies the proposed sections that form the basis of the final rule.

TABLE 2.—DERIVATION OF SECTIONS IN FINAL SUBPART A

Final Rule	2003 CGMP Proposal
§ 111.1 Who is subject to this part?	§ 111.1
§ 111.3 what definitions apply to this part?	§ 111.3
§ 111.5 Do other statutory provisions and regulations apply?	§ 111.5

B. Who Is Subject to This Part? (Final § 111.1)

Section 111.1 explains who is subject to the dietary supplement CGMP requirements. In brief, final § 111.1(a) states that you are subject to the dietary supplement CGMP requirements if you manufacture, package, label, or hold a dietary supplement. This requirement includes a dietary supplement you manufacture but that is packaged or labeled by another person, and a dietary supplement that is imported, offered for import in any State or Territory of the United States, the District of Columbia, or the Commonwealth of Puerto Rico. Final § 111.1(b), however, excludes certain persons from the rule. Specifically, § 111.1(b) states that the requirements pertaining to holding dietary supplements do not apply to you if you are holding those dietary supplements at a retail establishment for the sole purpose of direct retail sale to individual consumers. This section also states that a retail establishment does not include a warehouse or other storage facility for a retailer or a warehouse or other storage facility that sells directly to individual consumers.

This exclusion represents specific changes sought by the comments. We provide detail on the comments and our reasons for revising final § 111.1 in the following paragraphs.

(Comment 26) Some comments interpret the proposal as not applying to persons who perform labeling operations. For example, one comment claims

that proposed § 111.35(e), which would require manufacturers, packagers, and persons who hold dietary supplements to establish specifications, did not apply to “labelers” because the proposed definition of “you” did not expressly mention persons who label dietary supplements.

(Response) We disagree with the comments. Various provisions in the proposal expressly mentioned or pertained to labels and labeling operations (see, e.g., proposed §§ 111.20(c)(6) (which would require your physical plant to have separate or defined areas for packaging and label operations), 111.30(a) (which would impose certain requirements on automatic, mechanical, or electronic equipment used to “manufacture, package, label, and hold” a dietary supplement), 111.35(a) (which would require you to implement a system of production and process controls that cover, among other things, all stages of labeling dietary supplements), 111.37(a) (which would require you to use a quality control unit to ensure, among other things, your label operations are performed in a manner that prevents adulteration and misbranding), 111.40(b) and (c) (which would impose certain requirements on packaging and labels you receive and on persons who perform label requirements), and 111.70 (which would impose various requirements on packaging and label operations)). Although the proposed definition of “you” and proposed § 111.1 did not include the word “label” or “labeling,” we considered label operations to be part of a broader manufacturing process, and it would be illogical to interpret the proposal’s specific references to label operations as somehow being inapplicable to labelers simply because a proposed definition of “you” or a general “scope” provision did not mention labels or otherwise distinguish label operations from the broader context of manufacturing.

In any case, to correct such misinterpretation, we have revised § 111.1 to include the word “label.” Thus, under final § 111.1(a), you are subject to the dietary supplement CGMP requirements if you “manufacture, package, label, or hold a dietary supplement.” We also have made corresponding changes to other sections in this final rule; for example, we have revised the definition of “you” in final § 111.3 to state that “you” means “a person who manufactures, packages, labels, or holds” a dietary supplement, and we also have inserted the word “labeling” in the title to this final rule. We have not explained this change in the preamble each time it is made in the codified provision.

In addition, we refer to “label” and “labeling” in the context of CGMP requirements related to operations for ensuring the correct label is on the product. To help clarify that we are referring to labeling requirements in this final rule for labeling operations and not, for example, to the labeling requirements in part 101, we inserted the word “operations” in the title of part 111 to read “Current Good Manufacturing Practice in Manufacturing, Packaging, Labeling, or Holding Operations for Dietary Supplements.”

(Comment 27) Several comments ask for clarification about the rule’s applicability to different types of businesses and practices. Some comments ask for a clear listing of who is subject to the rule, stating that it is difficult to apply the rule’s specific provisions. According to these comments, the rule’s level of detail and inflexibility does not account for variations in manufacturing needs within the entire industry.

Several comments on various proposed sections ask who would be responsible for complying with CGMP requirements if more than one party was involved in the manufacturing, packaging, labeling, or holding of the

dietary supplement. For example, some comments ask whether consultants are subject to a specific proposed section; others ask who would be responsible if a firm employed another firm to handle packaging or labeling operations.

Other comments request clarification regarding the rule's applicability to distributors. Some comments claim that a person who holds and sells packaged products should not be subject to dietary supplement CGMP requirements. Other comments state that dietary supplement CGMPs should apply to distributors as well as manufacturers. These comments assert many supplement distributors are merely marketers who employ contract manufacturers. The comments said that, because marketers are the parties providing supplements to consumers, we should hold marketers responsible for their products and require marketers to ensure that their contract manufacturers adhere to CGMP requirements. These comments argue we should not permit marketers to transfer their responsibilities in delivering safe supplements. Other comments assert questions about the rule's applicability are underscored by typical dietary supplement labeling practices where the contact information listed on the product label pertains to the distributor/ marketer instead of the actual manufacturer.

Collectively, these comments raise a basic question as to which party or parties are responsible for complying with the dietary supplement CGMP requirements where more than one party is involved in the manufacture, packaging, labeling, or holding of that dietary supplement.

(Response) In the 2003 CGMP Proposal, we stated that it would apply to a wide variety of activities associated with the manufacture, packaging, and holding of a dietary supplement, including labeling, testing, quality control, holding, and distribution (68 FR 12157 at 12175). We stated under proposed

part 111 you would need to comply with those regulations directly applicable to the operations that you perform and provided examples (id.). All activities may not be performed by the same person. For example, a manufacturer may contract with another firm to package and label the dietary supplement in the containers used for distribution to consumers. Alternatively, a distributor may contract with one firm to manufacture a dietary supplement, and another firm to package and label the dietary supplement that the distributor ultimately distributes under its own name.

Under this final rule, you must comply with the CGMP requirements that apply to your operations related to the manufacture, packaging, labeling, and holding of dietary supplements. It is not practical to list all possible contractual relationships that persons may enter into in the manufacture of a dietary supplement, or to list all businesses or practices that may be subject to the requirements of this final rule in order for persons to know whether they are subject to requirements of this final rule. To provide additional clarity about how this rule may apply to various persons, we provide some examples in the following paragraphs.

A manufacturer that manufactures a dietary supplement, and then packages and labels and distributes the dietary supplement, is subject to all the requirements in this final rule. If that manufacturer contracts with another person to package and label the dietary supplement, then the packager/labeler is responsible for complying with the requirements for packaging and labeling operations, in addition to other relevant requirements. The packager/labeler, in this example, would need to comply, not only with the specific requirements related to packaging and labeling operations in subpart L, but also with the general requirements related to personnel, physical plant, quality

control, and other requirements that apply to that firm's operations. However the packager/labeler would not need to comply with requirements that do not apply to it; for example, the packager/relabeler would not have to conduct testing on the finished batch of dietary supplement since it does not manufacture the finished batch of dietary supplement.

A manufacturer who contracts with a person to do packaging and labeling, but who later distributes the packaged and labeled product, is ultimately responsible for the dietary supplement it releases for distribution. The manufacturer would be responsible for the CGMP requirements for the operations that it performs, including those related to the release of the product for distribution. For example, the manufacturer must determine whether the packaged and labeled dietary supplement it receives from the packager/labeler conforms to applicable specifications (final § 111.127(d)), and must approve the release of the packaged and labeled dietary supplement for distribution (final § 111.127(h)). Although the manufacturer is not performing the specific activities related to the packaging and labeling operations done by another person, the manufacturer has an obligation to know what and how such activities are performed so that it can make decisions related to whether the packaged and labeled product conforms to applicable specifications and whether to approve and release the product for distribution.

Some manufacturers may sell their finished batch of dietary supplement to a packager/labeler that the packager/labeler may package, label, and then hold and distribute. The manufacturer and packager/labeler would each be responsible for complying with the applicable CGMP requirements related to the operations that they perform. The manufacturer would not be responsible for the oversight of the packager/labeler, since the packager/labeler is not under

the control of the manufacturer and has control over the release of the packaged and labeled dietary supplement.

A manufacturer may decide to hire a contractor or a consultant for specific operations within the scope of the manufacturer's responsibilities under the final rule. For example, a manufacturer may hire a person to calibrate its equipment. The manufacturer is responsible for complying with the requirements related to its responsibilities, e.g., calibration requirements in this example, even though the manufacturer has hired another person to perform that job task.

In another example, a distributor who purchases a packaged and labeled dietary supplement and who then holds the product in a warehouse for distribution to another physical location is subject to the requirements related to its operations. The codified uses the word "hold" since it is a broad term which encompasses the activities of a distributor. Thus, the distributor would be responsible for complying with requirements in subpart M, *Holding and Distributing*, in addition to other requirements related to its operations (e.g., *Personnel, Physical Plant and Grounds*).

In cases where a distributor contracts with a manufacturer to manufacture a dietary supplement that the distributor then distributes under its own label, the distributor has an obligation to know what and how manufacturing activities are performed so that the distributor can make decisions related to whether the packaged and labeled product conforms to its established specifications and whether to approve and release the product for distribution.

(Comment 28) Some comments state that the proposed rule requirements would require the manufacturer to report adverse events to us, but would not require those who distribute the product and whose name is likely to be on

the product label, to report adverse events to us. The comments state that reports of adverse events submitted by consumers to those who distribute, but do not make, dietary supplements could be hidden from the public if such persons are not required to submit those reports to us.

(Response) The comments may have misinterpreted the proposed rule. The requirement to review and investigate a product complaint is distinct from any report about the product complaint to us. Reporting a complaint to us is not covered by these CGMP requirements and would be voluntary, unless the complaint is subject to the statutorily mandated reporting requirements for “significant adverse events” pursuant to the “Dietary Supplement and Non-Prescription Drug Consumer Protection Act” (Public Law 109–462), signed into law on December 22, 2006 (see discussion in section XX of this document).

Under the procedures that are set forth in subpart O, *Product Complaints* (see section XX of this document), a distributor and a manufacturer are both subject to the requirements related to the review and investigation of a product complaint that they receive.

(Comment 29) Some comments argue against including minimum CGMPs necessary for activities related to manufacturing, packaging, labeling, or holding dietary ingredients in the final rule. Several comments argue the proposed rule is overly broad and inconsistent with congressional intent. These comments question whether Congress intended that CGMP apply to persons involved in the manufacture, packaging, labeling, and holding of dietary ingredients. The comments also argue that, if the rule applies to dietary ingredient manufacturers, we would be establishing precedent and that we lack legal authority to regulate ingredients rather than the finished products themselves. The comments state that neither food CGMP nor drug CGMP offers

precedent or guidance on regulating ingredients. The comments argue those who provide dietary ingredients should be subject to the existing general food CGMP requirements in part 110 rather than to the dietary supplement CGMP requirements.

Several comments argue that many dietary ingredients are used in regular foods and in drugs as well as in dietary supplements. The comments argue, for some dietary ingredients, their use in dietary supplements represents a very small percentage of the dietary ingredient's worldwide usage. The comments say we should allow those who deal only with dietary ingredients to operate under one set of regulations, such as the general food CGMP requirements in part 110. According to these comments, we have not demonstrated either a failure of the current system or a compelling need to create different regulations for raw materials common to both the food and dietary supplement industries. The comments would revise the title of part 111 and proposed § 111.1 and make conforming revisions throughout the proposed rule to limit the rule's applicability to dietary supplements.

In contrast, other comments say the rule should apply to dietary ingredient manufacturers as well as to dietary supplement manufacturers. The comments state that excluding those who provide or supply dietary ingredients would mean those who have the greatest expertise in these goods would not be subject to dietary supplement CGMP requirements and thus fail to cover a crucial step in preventing the adulteration or contamination of dietary supplements. The comments argue that, for some dietary ingredients (especially raw botanical and agricultural goods), the most critical point in ensuring an ingredient's quality and purity is at time of harvest or creation, and that this is particularly true with new or original ingredients.

The comments state problems with dietary supplements often arise from substandard ingredients, and the difficulty in testing the properties of some botanical and other dietary ingredients at the in-process or finished product stage makes it necessary to include dietary ingredient manufacturers in the final rule. Furthermore, these comments assert a flexible testing scheme that they recommend (which emphasizes establishing specifications for components, relying on certificates of analysis from qualified suppliers, qualifying component suppliers, and establishing written procedures, with testing of finished batches serving as a check on the overall manufacturing process) makes it important to regulate dietary ingredient manufacturers.

Other comments suggest we issue a separate or modified set of CGMP requirements that would apply to persons who manufacture, package, label, or hold dietary ingredients. These comments say the proposed rule does not work for all dietary ingredients, especially those converted from non-food grade to food grade during the manufacturing process. These comments said the rule should be modified for dietary ingredients.

(Response) Two issues seem to be raised by these comments: (1) Whether dietary ingredients are within the scope of this final rule and (2) whether dietary ingredient manufacturers are subject to this final rule. Dietary ingredients are included within the scope of this final rule but dietary ingredient manufacturers are not necessarily subject to this rule. The definition of "component" in this final rule includes "any substance intended for use in the manufacture of a dietary supplement including those that may not appear in the finished batch of the dietary supplement. Component includes dietary ingredients (as described in section 201(ff) of the act) and other ingredients" (final § 111.3). The proposed rule, § 111.3, recognized that

“dietary ingredients” are “components” (68 FR 12157 at 12176) (describing how dietary ingredients would fall within the proposed definition of “component”).

There are specific requirements in this final rule that relate to components, and thus dietary ingredients, that are used in the manufacture of a dietary supplement. For example, final § 111.70(b) requires you to establish certain component specifications. Such requirements would include specifications for dietary ingredients as “components.” It is important to control the components used in the manufacture of dietary supplements to ensure consistency and to ensure the quality of the dietary supplement. Since dietary ingredients are considered components, the various requirements apply to dietary ingredients as part of the production and process control. Therefore, we disagree to the extent comments were suggesting that there should be no CGMP requirements related to the dietary ingredients used by a manufacturer in the manufacture of dietary supplements.

Dietary ingredients are included within the meaning of “component.” In those requirements in the proposed rule where “component” encompasses “dietary ingredient” we are, in the final rule, removing “dietary ingredient” in those requirements and only refer to “component.” Given the scope of the final rule, it is redundant to refer to both “component” and “dietary ingredient” where the latter is subsumed in the former.

In response to comments that questioned the need to include manufacturers of dietary ingredients within the scope of part 111, we have made changes to the scope of the rule, as applied to dietary ingredient manufacturers. As we explain more fully in our discussion of final §§ 111.70, 111.73, 111.75, and 111.77 (see section X of this document), after considering

comments about the overall production and process control system, we revised the final rule's approach to ensuring product quality. This approach emphasizes that it is important to ensure the quality of the dietary supplement throughout the production and process control system. This approach emphasizes establishing specifications for components and ensuring those specifications are met. You may rely on a certificate of analysis for specifications (except for the identity of the dietary ingredient) only if you satisfy certain criteria, which include qualifying the supplier of the components. With this approach, the goal of ensuring the quality of dietary supplements can be achieved without applying the rule specifically to persons who manufacture, package, label, or hold dietary ingredients that will be further processed as a dietary supplement by other persons.

Consequently, we revised § 111.1 by deleting "dietary ingredient." Therefore, those who manufacture, package, label, or hold dietary ingredients are not subject to the final rule. To illustrate, assume you manufacture a dietary ingredient and sell that bulk dietary ingredient to Company X. Company X then utilizes the bulk dietary ingredient in a dietary supplement. Under final § 111.1(a), you would not be subject to these dietary supplement CGMP requirements because you are not manufacturing a dietary supplement, rather you are manufacturing a dietary ingredient for further incorporation into a dietary supplement by Company X. If, however, you sell herbs in bulk to Company X, and Company X simply packages the herbs into smaller units for sale as a dietary supplement, you would be subject to the dietary supplement CGMP requirements because you are manufacturing a dietary supplement that Company X is simply packaging and labeling, and not further processing into a dietary supplement. In other words, in the latter example, you would have

acted as a manufacturer whose finished product is simply repackaged or relabeled.

Under final § 111.1(a) persons engaged solely in activities relating to the harvesting, storage, or distribution of raw agricultural commodities that will be incorporated into a dietary supplement by others are not included within the scope of the rule as a dietary supplement manufacturer. This is because those persons simply “supply” a component (i.e., the raw agricultural commodity) that another person will process into a dietary supplement; thus you do not manufacture, package, label, or hold a dietary supplement.

Note, too, that if you manufacture and supply a component directly to consumers as a dietary supplement, you would be considered a dietary supplement manufacturer within the scope of final § 111.1(a). Likewise, if you manufacture a component and sell part of the batch to another person who, in turn, will further process the component as a dietary supplement and sell the remainder of the batch to consumers as a dietary supplement, you would be subject to the dietary supplement CGMP requirements, as a manufacturer, for the product sold to consumers and not subject to an exclusion under final § 111.1(b), discussed in this section. In other words, final § 111.1(a) refers to the nature of your activity, and simply engaging in some activities that do not bring you within the scope of the final rule does not necessarily mean that all your activities are outside the scope of the final rule.

We do not agree, as some comments suggested, that we need to issue a separate or modified set of CGMP requirements for dietary ingredients. That is because there are adequate controls established in this final rule for the use of dietary ingredients used by the manufacturer of a dietary supplement. However, if you manufacture, package, label, or hold dietary ingredients that

will be further processed as a dietary supplement by another person, you must comply with food CGMP requirements in part 110. A dietary ingredient is a food under section 201(f) of the act, as a food, or as a component of food. Because the final rule gives manufacturers an incentive to qualify suppliers of dietary ingredients, persons who manufacture, package, label, or hold dietary ingredients may wish to familiarize themselves with these dietary supplement CGMP requirements and use them in manufacturing, packing, labeling, or holding operations for dietary ingredients.

(Comment 30) Some comments argue if the final rule ultimately covers dietary ingredient suppliers then we should clarify what constitutes a “consumer.” According to these comments, dietary ingredient suppliers do not typically supply their products directly to those individuals who will ultimately consume or ingest them. Thus, “consumers” of dietary ingredients are other companies, not individuals. The comments express concern about the possible application of proposed § 111.95 which would require procedures for handling complaints.

(Response) The final rule applies only to persons who manufacture, package, label, or hold dietary supplements and are not subject to an exclusion in final § 111.1. However, as explained in the previous response to comment 29, if a dietary ingredient manufacturer also supplies or sells a dietary ingredient as a dietary supplement, such a manufacturer would be subject to final § 111.1(a) and subject to all relevant dietary supplement CGMP requirements.

Some comments expressed concern about dietary ingredient manufacturers having to comply with proposed § 111.95 on product complaints. If a dietary ingredient manufacturer receives a product complaint, we encourage the

manufacturer to evaluate the complaint to determine if it may involve a problem with the manufacture of the dietary ingredient. In addition, we encourage the dietary ingredient manufacturer to notify the dietary supplement manufacturer so that it can review the complaint and investigate, as needed.

(Comment 31) Several comments question the proposal's applicability to persons who sell packaged products or seek clarification as to whether the rule applies to dietary supplement manufacturers that operate from homes and those that distribute product to other distributors.

(Response) To the extent that the comments question whether retailers or individuals who sell dietary supplements directly to individual consumers are subject to the dietary supplement CGMP requirements, we have revised the final rule by creating a new § 111.1(b) which states that: "The requirements pertaining to holding dietary supplements do not apply to you if you are holding those dietary supplements at a retail establishment for the sole purpose of direct retail sale to individual consumers. A retail establishment does not include a warehouse or other storage facility for a retailer or a warehouse or other storage facility that sells directly to individual consumers." This means, for example, if you operate a storefront retail establishment where you stock dietary supplements on your shelves for purchase by individual consumers, we do not consider you to be "holding" those dietary supplements in a manner that would require you to comply with the holding provisions in this final rule. Sale to individual consumers, where you are not storing bulk dietary supplements as one would in a warehouse or storage facility, does not fall within the manufacturing, packaging, labeling, or holding activities that would subject you to dietary supplement CGMP requirements.

However, if you operate storefront retail establishments, and those retail establishments obtain their stocks from your warehouse, we would consider your warehouse operations to be “holding” dietary supplements and expect your warehouse operations to comply with the rule’s holding requirements. Such distribution is no different than other warehouse operations that are normally subject to CGMP requirements. Consequently, to distinguish between “holding” dietary supplements for retail sale to consumers and “holding” dietary supplements in a warehouse for further distribution, final § 111.1(b) limits the exclusion to persons holding dietary supplements “at a retail establishment for the sole purpose of direct retail sale to individual consumers.” Final § 111.1(b) also makes it clear that a retail establishment does not include a warehouse or other storage facility that a retailer uses to hold the dietary supplements or an operation that sells directly to consumers, but that itself distributes the product to the consumer from a warehouse or storage facility and not from a storefront retail establishment.

(Comment 32) Many comments question the rule’s applicability to various practitioners such as herbalists, acupuncturists, naturopaths, and other health care providers who prepare individualized herbal formulas for specific individuals on a case-by-case basis. Most comments say such practitioners should not be covered by the rule. These comments give various reasons to justify their position, including:

- These practitioners do not broadly sell products;
- These practitioners make very small quantities of individualized formulas, and can therefore be very selective as to the quality of ingredients used;

- The testing and storage requirements of each finished batch cannot apply to a small dispensary where several different modified herbal formulas are prepared each day;
- Based on the projected costs to implement CGMPs, it would be virtually impossible for an individual practitioner or university clinic to develop the necessary quality control unit, maintain reserve samples, maintain the required paperwork, or retrofit clinics to comply with the rule;
- Many States regulate or license these practitioners, so further Federal regulation is unnecessary;
- Some practitioners do not consider themselves to be manufacturers;
- In an analogous situation, compounding pharmacists are not required to comply with drug CGMPs; and
- Despite the growing number of such practitioners, there is no proof that greater harm has occurred to the general public from the herbs these practitioners sell.

(Response) We stated in the 2003 CGMP Proposal (68 FR 12157 at 12175) that we declined to exempt herbalist practitioners from the proposed rule. We continue to believe that the risks of adulteration are not eliminated just because the practitioner is an herbalist, and therefore, such an exemption should not be included in this final rule. However, after further consideration, we have determined that it would be appropriate for us to consider the exercise of our enforcement discretion in deciding whether to apply the requirements of this final rule to certain health care practitioners, such as herbalists, acupuncturists, naturopaths, and other related health care providers.

We find it noteworthy that the comments identified two potential safeguards that could support the exercise of our enforcement discretion on

whether to apply the requirements of the final rule to certain practitioners:

(1) Adequate training in the professional practice and (2) an individual client and practitioner relationship. For example, comments claimed that the practitioners receive adequate training to formulate dietary supplements and that they provide the dietary supplements to individuals in the course of a one-on-one consultation on the premises of the practitioner. One comment from a practitioner states that she received her training from an accredited 4-year university and it included didactic and clinical training in acupuncture and Chinese herbs. Another comment from an organization provides detailed training guidelines for practitioners, including 1,600 hours of training, 400 hours of which should include clinical work. Moreover, many comments also assert that the practitioners are different from dietary supplement manufacturers because they formulate the dietary supplements in the course of a one-on-one consultation at their premises. That enables them to ensure the formulations are made to meet the specific needs of the individuals.

We believe that a one-on-one consultation by a practitioner who is adequately trained in their profession may not necessitate the same types of controls as we are establishing in this final rule for manufacturing activities that are on a larger scale. Such a practitioner may make some formulations in advance of the consultation and still make the formulations in very limited quantities for the individual client. We believe that it would be appropriate to consider the exercise of our enforcement discretion, on a case-by-case basis, to determine whether to apply the requirements of this final rule to such persons.

We do not expect the number of those subject to the consideration of our enforcement discretion to be very large. Many products that are manufactured

by practitioners would not necessarily be considered to be dietary supplements (e.g., certain products used by traditional Asian medicine practitioners).

Further, we are not considering exercising our enforcement discretion with respect to practitioners who prepare batches of herbs and sell them to individual consumers without determining whether the dietary supplement is appropriate for each consumer's needs in a one-on-one personal consultation, or those that prepare batches of a dietary supplement for which there is a known or suspected safety concern.

(Comment 33) Several comments asked us to exempt academic institutions that provide training for therapeutic disciplines that use, for example, herbal formulas in their practice regardless of whether the dietary supplements they produce enter into interstate commerce. Specifically, these comments would revise the final rule to state that it does not apply "to academic institutions that provide training in dispensing of nutritional or herbal products and formulas related to courses in therapeutic disciplines that provide such products and formulas as a part of their therapy, for example, naturopathy, herbalism, traditional Chinese medicine, and acupuncture."

(Response) Similar to what we stated in response to comment 32, we believe that it may be appropriate to consider the exercise of our enforcement discretion in circumstances where an academic institution's actions are similar to those of a practitioner who is adequately trained in their profession and who provides dietary supplements within the context of an individual client and practitioner relationship. In general, it is not our policy to inspect an academic institution that provides training for therapeutic disciplines that use, for example, dietary supplements in their practice. We intend to consider the exercise of our enforcement discretion in those situations where there is a one-

on-one consultation that includes a practitioner with adequate training. We intend to issue guidance to further clarify how the agency intends to exercise its enforcement discretion on the application of this final rule to certain academic institutions.

(Comment 34) Several comments discuss the position taken by certain nations, notably Australia and Canada, that have developed CGMP requirements and related guidance for botanicals. According to these comments, these nations recognize that there are various types of practitioners who sell herbs and herbal preparations in a clinical setting, and do not consider such persons to be manufacturers. The comments ask us to follow the example of these nations.

(Response) We intend to consider the positions taken by other nations to inform us in our decisionmaking in any future guidance on how we intend to exercise our enforcement discretion on the application of this final rule to certain practitioners.

(Comment 35) Many comments say we should define when a dietary supplement will be said to have entered interstate commerce. The comments state herbal practitioners (and academic institutions) often purchase source herbs from outside their State, even if they prepare these herbs for their specific customers within the State. These comments request we clarify that the rule does not apply to herbs purchased out of State if prepared for local use. Other comments request clarification regarding clients who have moved across State lines, yet maintain a relationship with an herbalist practitioner.

(Response) In section V of this document we explain the interstate and intrastate issue related to the final rule.

(Comment 36) A few comments assert individual practitioners and practitioner organizations often are unaware of the opportunity to comment on CGMP or regulatory issues. Therefore, the comments say these practitioners and organizations often fail to provide comment or otherwise participate in rulemaking and say we should give these practitioners and practitioner organizations a chance to comment.

(Response) We provided many opportunities for comment and, therefore, we decline to adopt the comments' suggestion. As we discuss in section I of this document, we published an ANPRM concerning dietary supplement CGMPs on February 6, 1997 (62 FR 5700); the 1997 ANPRM provided an opportunity for public comment. On March 7, 2003, we issued a Talk Paper, along with other background documents, announcing the issuance of a proposed dietary supplement CGMP rule. We made the proposed rule available when it went on display (before it published) in the **Federal Register** on March 13, 2003 (68 FR 12157), and, again, provided an opportunity for public comment. We also held public meetings on April 29, 2003, in College Park, MD and on May 6, 2003, in Oakland, CA. We also held a public meeting (via satellite downlink) on May 9, 2003, with viewing sites at our district and regional offices throughout the country. Thus, we provided numerous opportunities for interested persons to learn about the rule and to submit comments or otherwise participate in the rulemaking process. Consequently, we decline to provide yet another opportunity for comment.

(Comment 37) The preamble to the 2003 CGMP Proposal noted that comments submitted in response to our 1997 ANPRM state we should not distinguish between dietary supplements made in the United States and those made in a foreign country (68 FR 12157 at 12174). Although we agreed with

the comments and made no distinction between foreign and domestic firms in the proposed rule, we invited comment on how we might ensure dietary ingredients and dietary supplements exported to the United States have been manufactured, packaged, labeled, and held consistent with part 111 (68 FR 12157 at 12175).

Several comments argue the rule should apply to foreign firms as well as domestic manufacturers to ensure a “level playing field” and to protect American consumers. Some comments say we should work with foreign countries to harmonize our requirements and thus avoid potential trade disputes under international trade agreements such as the General Agreement on Tariffs and Trade. Other comments suggest compliance by foreign firms could be achieved through the use of third party certification programs, such as the dietary supplement verification program administered by USP, or the adoption of importer verification provisions similar to those used in our HACCP requirements for seafood (see § 123.12).

In contrast, another comment says we should inspect foreign firms to ensure compliance, whereas other comments claim we lack jurisdiction over foreign firms.

(Response) We are amending proposed § 111.1 to clarify the regulation’s applicability to foreign firms. We explain in this section how we may enforce the rule against foreign firms. We, however, are not making any changes in response to the comments calling for the harmonization of the rule with foreign rules because this request is beyond the scope of the final rule.

In response to comments, and for clarification, we have revised final § 111.1(a) to clarify that the regulation applies to the extent that you manufacture, package, label, or hold a dietary supplement, including a dietary

supplement imported or offered for import in any State or Territory of the United States, the District of Columbia, or the Commonwealth of Puerto Rico.

With respect to the comments requesting that we make clear our position for enforcing the rule against foreign firms, we explain our position as follows. Section 801(a) of the act (21 U.S.C. 381a) authorizes us to refuse admission of an imported food if it appears from the examination of such samples or otherwise that such article is, among other things, adulterated. A foreign firm's refusal to allow us to obtain records via an inspection for CGMP purposes, as required by final § 111.610 (for the dietary supplements the foreign firm offers for import into the United States), would create the appearance that such imported dietary supplements are adulterated under section 402(g) of the act, and thus, could lead to a refusal of admission under section 801(a) of the act.

Foreign firms who ship to the United States must operate under conditions that satisfy our regulations, including the requirement that records be made available during the course of an FDA inspection. We note that except in circumstances where there is a public health emergency or we receive information that would indicate the appearance of adulteration of products shipped to the United States, foreign inspections are generally scheduled well, e.g., weeks, in advance. Thus, we believe that taking action under section 801 of the act is appropriate if companies do not accommodate our inspectional request.

C. What Definitions Apply to This Part? (Final § 111.3)

Section 111.3 defines various terms that we use in the final rule and notes that definitions or interpretations of terms in section 201 of the act also apply. In general, we adopted the definitions that we proposed, although, in some cases, we deleted words or concepts as a result of other changes we made to

the final rule. We have added a definition of “quality” for purposes only of this final rule.

A recurring change we made is the deletion of the words “dietary ingredient” in several definitions. In some cases, the use of the words “dietary ingredient” was redundant to the use of “component” and thus not necessary in the final rule. Because a “dietary ingredient” is subsumed within the definition of “component,” as explained in our response to comment 29, we deleted “dietary ingredient” in those definitions where “component” was used to avoid redundancy.

In other provisions, we deleted “dietary ingredient” from the definition because the use of those words was no longer necessary given the narrowing of the scope of the rule as it applies to dietary ingredient manufacturers (explained in the response to comments 29 and 30). For example, we deleted “dietary ingredient” from the proposed definition of “ingredient” that referred to the “manufacture of a dietary ingredient or dietary supplement” and the “finished batch of the dietary ingredient or dietary supplement.” We did not need to state “manufacture of the dietary ingredient” or refer to “finished batch of dietary ingredient” because dietary ingredient manufacturers that only supply such ingredients to other persons for processing into a dietary supplement are not subject to the final rule.

We discuss changes to the definitions, other than the changes we have made globally such as the deletion of “dietary ingredients,” the change from “include, but not limited to” to “includes” or “include,” the addition of labels and labeling, and the deletion of the word “quality” from the phrase “identity, purity, quality, strength, and composition,” as well as comments asking us to

define more terms or to delete certain definitions, in more detail in the following paragraphs.

1. Actual Yield

The final rule defines “actual yield” as “the quantity that is actually produced at any appropriate step of manufacture or packaging of a particular dietary supplement.”

We received no substantive comments to the proposed definition.

2. Batch

The final rule defines “batch” as “a specific quantity of a dietary supplement that is uniform, that is intended to meet specifications for identity, purity, strength, and composition, and that is produced during a specified time period according to a single manufacturing record during the same cycle of manufacture.”

This definition differs from the proposed definition of “batch” by stating that a batch is a specific quantity of a dietary supplement that is “uniform.”

We inserted the word “uniform” in response to comments asking that we define “lot” to be consistent with “batch.” We explain our reasons for harmonizing the definitions and for inserting “uniform” into the definition of “batch” in the response to comment 42 of this document.

We discuss the comments on our proposed definition of “batch” and our changes to the definition in our responses to the following comments.

(Comment 38) Several comments ask us to clarify what the “same cycle of manufacture” is in the definition of “batch.” One comment asks if it meant the same product made with the same lot(s) of raw materials regardless of how many days it took to produce the batch, or if it meant a quantity produced in 1 day. The comment also asks whether batches produced on consecutive

days, using the same formula, can be considered to be the same batch with respect to the proposed testing requirements if the quality control unit determined that different lots of raw materials are equivalent (e.g., by meeting all specifications).

(Response) The “same cycle of manufacture” refers to a process during which equipment remains dedicated to the manufacture of the batch. The terms do not limit you to any particular time period or require you to operate equipment continuously until you have completed the “same cycle of manufacture.” The “same cycle of manufacture” also does not limit the number of lots of components you use.

You may consider, as one batch, a product produced using different lots of raw materials where the production of the batch is a continuous process on a dedicated line. However, for each component that you use in the manufacture of the batch of dietary supplement, you would need to establish specifications under final § 111.70, determine whether these specifications are met under final § 111.73, and ensure that these component specifications are met using the criteria under final § 111.75. Further, you may not consider different batches of product produced on consecutive days using the same formula to be the same batch for purposes of testing requirements. The term “different batches” suggests that the production is not a continuous process on a dedicated line.

3. Batch Number, Lot Number, or Control Number

The final rule defines these terms as “any distinctive group of letters, numbers, or symbols, or any combination of them, from which the complete history of the manufacturing, packaging, labeling, and/or holding of a batch or lot of dietary supplements can be determined.”

We received no substantive comments on the definition. We added the word “and” before “or” to emphasize that the history of each activity must be able to be determined.

4. Component

The final rule defines “component” as “any substance intended for use in the manufacture of a dietary supplement, including those that may not appear in the finished batch of the dietary supplement. Component includes dietary ingredients (as defined in section 201(ff) of the act) and other ingredients.”

The definition of component now refers only to the manufacture of a dietary supplement (whereas the proposal also referred to the manufacture of dietary ingredients). We also made a nonsubstantive, editorial revision in the last sentence to put parentheses around the reference to section 201(ff) of the act and to change the word order so that “component” includes “dietary ingredients * * * and other ingredients.” (The proposed definition had “components” including “ingredients and dietary ingredients.”)

(Comment 39) Some comments would distinguish among “raw material,” “components,” and “starting material” because the comments said that defining “component” to include all these materials is confusing. One comment adds that many starting materials are not food grade or approved food ingredients until they have been processed. One comment states the term “raw material” is typically used to describe the materials (such as dietary ingredients, fillers, and processing aids) that will be used to make the final product. The comment further states “component” is typically used to describe the specific items used to assemble the finished product for the end user. The components would include packaging components such as bottles, caps, and

labels, as well as the bulk dietary supplement. This comment also suggests that we use the term “starting material” to distinguish substances used in the manufacture of dietary ingredients from substances used in the manufacture of dietary supplements.

(Response) We decline to revise the rule as suggested by the comments. There may be differences in how components are referred to by certain manufacturers and how we refer to it in this final rule. However, for purposes of this final rule we refer to all substances used in the manufacture of dietary supplements as “components,” whether or not those substances appear in the finished product.

Please note that, although ingredients are “components” under our definition, not all components are ingredients. For example, a solvent used to make an herbal extract is not an ingredient when it is removed from the extract by a process such as drying, because the solvent was not intended to be present in the finished dietary supplement. However, the solvent would be a “component” because it was used in the manufacture of the dietary supplement.

As for materials that might not be food grade or approved food ingredients until processing, see the discussion in response to comment 240 in section XII of this document.

(Comment 40) Several comments express concern that “component” could be interpreted to mean any constituent present in a botanical extract or other natural product. The comments say a single botanical can contain tens of thousands of constituents or metabolites and that chemists have not identified all constituents of a single botanical. According to the comments, the cost of testing for all constituents would exceed a product’s total annual revenues.

(Response) In general, we would consider the botanical extract or the other natural product to be the “component” as defined in this final rule rather than consider that all the various chemical substances contained in the botanical extract or other natural product are components. Thus, if you are manufacturing a dietary supplement that is intended to provide a certain substance (e.g., vitamin C) and you add a natural product which is intended to supply the vitamin C (e.g., vitamin C in the form of rosehips), we would consider the natural product (e.g. rosehips that contain a certain amount of vitamin C) to be a component which must be listed in the master manufacturing record. The component specifications for the rosehips must include a specification for the strength of the substance (e.g., vitamin C) in whatever amount you determine is necessary to meet the specification for the strength of the vitamin C in the finished batch of dietary supplement. Under final § 111.70, we expect you to establish specifications for the natural product and ensure that the specifications are met. As an example relevant to an extract, if you are manufacturing a dietary supplement that is intended to provide a certain amount of vitamin C that derives from the natural product rosehips, and the substance that you purchase from a supplier to add as a component is a purified extract of rosehips (rather than rosehips themselves), we would consider the purified extract to be a component (as an ingredient). The component specifications for the purified extract must include a specification for the strength of the substance (i.e., vitamin C) in whatever amount you determine is necessary to meet the specification for the strength of the vitamin C in the finished batch of dietary supplement. However, in this example “rosehips” would not be considered a component, because “rosehips” is not what you added.

5. Contact Surface

The final rule defines “contact surface” as “any surface that contacts a component or dietary supplement, and those surfaces from which drainage onto the component or dietary supplement, or onto surfaces that contact the component or dietary supplement, occurs during the normal course of operations.” The final rule lists containers, utensils, tables, contact surfaces of equipment, and packaging as examples of “contact surfaces.”

We did not receive any substantive comments on the proposed definition. We deleted “ordinarily” from “ordinarily occurs during the normal course of operations” because “ordinarily” is redundant to “normal.”

6. Ingredient

The final rule defines “ingredient” as “any substance that is used in the manufacture of a dietary supplement and that is intended to be present in the finished batch of the dietary supplement. An ingredient includes, but is not necessarily limited to, a dietary ingredient as defined in section 201(ff) of the act.” We did not receive any substantive comments on this definition. We made a nonsubstantive, editorial change to replace “finished dietary supplement” with “finished batch of the dietary supplement.”

(Comment 41) One comment says we should define “ingredient” better to ensure consistent interpretation of CGMP at all levels throughout the dietary supplement industry.

(Response) We disagree with the comment. We believe the definition is adequate, including as it does both dietary ingredients as described in section 201(ff) of the act and other ingredients that do not fit that description, such as an emulsifier used to establish a uniform dispersion in a liquid dietary supplement or a color additive used to color a capsule. Moreover, the comment

did not explain or specify which aspects of the proposed definition should be revised or explain why the proposed definition would lead to inconsistent interpretations of CGMP.

7. In-Process Material

The final rule defines “in-process material” as “any material that is fabricated, compounded, blended, ground, extracted, sifted, sterilized, derived by chemical reaction, or processed in any other way for use in the manufacture of a dietary supplement.”

We did not receive any substantive comments on the proposed definition.

8. Lot

The final rule defines “lot” as “a batch, or a specific identified portion of a batch, that is uniform and that is intended to meet specifications for identity, purity, strength, and composition; or, in the case of a dietary supplement produced by continuous process, a specific identified amount produced in a specified unit of time or quantity in a manner that is uniform and that is intended to meet specifications for identity, purity, strength, and composition.”

The final rule differs from the proposed definition in that the proposed definition of “lot” would have the batch or specific identified portion of a batch be intended to have “uniform identity, purity, quality, strength, and composition.”

(Comment 42) One comment agrees with the proposed definition for “lot,” but several other comments would revise the definition to be more consistent with the proposed definition of “batch.” Specifically, the comments note the proposed definition of “batch” would refer to a quantity of dietary supplement that is “intended to meet specifications for identity, purity, quality, strength

and composition,” whereas the proposed definition of “lot” would refer to a batch or specific identified portion of a batch that is “intended to have uniform identity, purity, quality, strength, and composition.” The comments would revise the definition of “lot” by deleting the phrase “intended to have uniform” and inserting the phrase “intended to meet specifications for” in order to make the definitions of “batch” and “lot” consistent.

(Response) We agree that the definitions for “batch” and “lot” should be consistent, but we disagree with the comments’ suggestion to delete the term “uniform” from the definition of “lot.” The attributes of a lot or batch should be uniform throughout the lot or batch and meet established specifications for those attributes. If samples from a lot or batch were tested for appropriate specifications of identity, purity, strength, and composition, the attributes should be consistent throughout the sample and be uniform from sample to sample regardless of whether the test samples are taken from the beginning, middle, or end of the lot or batch. Consequently, we revised the definition of “lot” to state, in relevant part, that a “lot” is a batch or specific identified portion of a batch that “is uniform and that is intended to meet specifications for identity, purity, strength, and composition” or, for dietary supplements produced by a continuous process, a specific identified amount produced in a specified unit of time or quantity in a manner that is uniform and that is intended to meet specifications for identity, purity, strength, and composition.”

Similarly, we revised the definition of “batch” so that it states, in relevant part, that a “batch” is a specific quantity of a dietary supplement “that is intended to meet specifications for identity, purity, strength, and composition.”

These revisions make the definitions of “batch” and “lot” consistent.

9. Microorganisms

The final rule defines “microorganisms” as “yeasts, molds, bacteria, viruses, and other similar microscopic organisms having public health or sanitary concern.” It adds that the definition includes species that: (1) May have public health significance; (2) may cause a component or dietary supplement to decompose; (3) indicate that the component or dietary supplement is contaminated with filth; or (4) otherwise may cause the component or dietary supplement to be adulterated.

(Comment 43) One comment would revise the definition to identify specific microorganisms that have public health or sanitary concern (i.e., *Salmonella* species, *Escherichia coli*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus*). The comment says this would be consistent with USP requirements.

(Response) We disagree with the comment. A list of specific microorganisms could easily become outdated as new pathogens emerge, and constantly issuing new rules to revise the list would be both inefficient and impractical.

(Comment 44) One comment expresses concern that the proposed definition for microorganisms would include microorganisms that are a natural part of the ecology of all natural products. The comment says certain levels of microorganisms are expected on botanical raw materials (i.e., those naturally occurring or introduced through organic cultivation techniques) and that many do not present a public health risk. The comment expresses concern that nonpathogenic microorganisms that are not a public health risk would be a “sanitary” concern that would render a product adulterated. The comment

argues there should be little concern about the presence of microorganisms that present no public health consequence, and so we should revise the definition accordingly. The comment further discusses the difficulties in “sterilizing” botanicals to render them free of microorganisms associated with insanitary conditions. The comment notes that some international organizations have established “upper limits” for these organisms for botanical supplements, which, in the comment’s opinion, represent more realistic standards than trying to attain a “sterile” botanical supplement.

(Response) We disagree with the comment. We do not interpret the definition of “microorganism” as making the presence of nonpathogenic microorganisms that are not a public health risk a “sanitary concern” that would render a product adulterated. Instead, we interpret the definition as saying that microorganisms of public health significance and microorganisms presenting sanitary concerns are “microorganisms” under this rule. These are the types of microorganisms that may cause a component or dietary supplement to become adulterated.

As for upper limits on microbial contamination, the comment offered no suggested limits, and we decline to establish such limits in this rule. The final rule requires manufacturers to establish limits for those types of contamination that may adulterate or lead to adulteration of components or dietary supplements. Thus, for example, a manufacturer of a botanical dietary supplement would have to determine what, if any, microorganisms are likely or certain to be present and establish limits, as appropriate to prevent adulteration of the finished batch of the dietary supplement.

We have modified the word “have” with the word “may” to indicate that the determination or evaluation of whether there is a “public health

significance” is not made after the fact. There does not have to be a factually established determination of public health significance for you to conclude that the microorganisms “may adulterate” the dietary supplement. The change from “could cause” to “may cause” is to be consistent with the previous change to “may have.”

10. Must

The final rule explains that the word “must” is “used to state a requirement.”

(Comment 45) One comment would revise the definition to say that the term “must” be used to state mandatory requirements “unless shown to be inapplicable or replaced by an alternative demonstrated to provide at least an equivalent level of quality assurance.”

(Response) We decline to revise the rule as suggested by the comment. The comment’s revision would undermine the reasons for issuing a rule. Rules create enforceable requirements. It is not clear, nor did the comment discuss, how we could enforce the requirements in this final rule if firms were able to avoid a particular requirement by declaring them to be “inapplicable” or substituting alternatives which they felt they had demonstrated were “at least an equivalent level of quality assurance.” There would be inconsistency in the general CGMP practices used within the dietary supplement industry and uncertainty as to whether the process and production controls ensure the quality of the dietary supplement. Consequently, we decline to revise the rule as suggested by the comment.

We have, however, made a nonsubstantive, editorial change to the definition so that “must” is used to state “a requirement.” The proposed

definition had referred to “mandatory requirements.” Since a requirement by its nature is mandatory, the word “mandatory” is unnecessary.

11. Pest

The final rule defines “pest” as “any objectionable insect or other animal, including birds, rodents, flies, mites, and larvae.”

We did not receive any substantive comments on this definition. However, on our own initiative, we made nonsubstantive, editorial changes to delete the words, “but not limited to” after “including” and to place the word “animals” in the singular.

12. Physical Plant

The final rule defines “physical plant” as “all or any part of a building or facility used for or in connection with manufacturing, packaging, labeling, or holding a dietary supplement.”

We received no substantive comments on this definition. The final rule is substantially similar to the proposed rule’s definition of “physical plant.” We added “any” and placed “part” in the singular to clarify that individual parts of a building or facility are subject to the CGMP requirements.

13. Product Complaint

The final rule defines “product complaint” as “any communication that contains any allegation, written, electronic, or oral, expressing concern, for any reason, with the quality of a dietary supplement, that could be related to current good manufacturing practice. Examples of product complaints are: Foul odor, off taste, illness or injury, disintegration time, color variation, tablet size or size variation, under-filled container, foreign material in a dietary supplement container, improper packaging, mislabeling, or dietary

supplements that are superpotent, subpotent, or contain the wrong ingredient, or contain a drug or other contaminant (e.g., bacteria, pesticide, mycotoxin, glass, lead).”

This definition modifies the proposed rule’s definition of “consumer complaint,” which would define such a complaint as any “communication that contains any allegation, written or oral, expressing dissatisfaction with the quality of a dietary supplement related to good manufacturing practices. Examples of product quality related to good manufacturing practices are: Foul odor, off taste, superpotent, subpotent, wrong ingredient, drug contaminant, other contaminant (e.g., bacteria, pesticide, mycotoxin, glass, lead), disintegration time, color variation, tablet size or size variation, under-filled container, foreign material in a dietary supplement container, improper packaging, or mislabeling. For the purposes of this regulation, a consumer complaint about product quality may or may not include concerns about a possible hazard to health. However, a consumer complaint does not include an adverse event, illness, or injury related to the safety of a particular dietary ingredient independent of whether the product is produced under good manufacturing practices.”

We explain the reasons for revising the proposed definition in our response to the following comments.

(Comment 46) Some comments would broaden the definition of consumer complaint to include complaints from dietary ingredient suppliers. One comment would change “consumer complaint” to “customer complaint.”

(Response) As discussed in section VI of this document, the final rule does not apply to those who only manufacture dietary ingredients. However, we encourage such firms that receive complaints about a dietary supplement to

share those complaints with those in the manufacturing chain associated with that dietary supplement's manufacture so others may take corrective action as needed. Those who engage in the manufacture of a dietary supplement, including manufacturing, packaging, labeling, and holding operations, are responsible for complying with this final rule's product complaint requirements.

Furthermore, we encourage packagers, labelers, and distributors who receive a product complaint to notify those in a dietary supplement's manufacturing chain about product complaints they receive or they, themselves, generate that may relate to operations outside the packagers', labelers', or distributors' control. For example, a distributor who purchases a dietary supplement in bulk for packaging and labeling may complain about product quality to the dietary supplement manufacturer. The manufacturer who receives the complaint must then take appropriate action to determine whether the complaint involves a possible failure of a dietary supplement to meet any CGMP requirements. Thus, the final rule revises the term "consumer complaint" to "product complaint" to emphasize that the complaint is about the product regardless of the complaint's source.

(Comment 47) One comment disagrees that "disintegration time" and "tablet size" are appropriate examples of complaints about product quality specifications.

(Response) We disagree with this comment. Complaints about disintegration time or tablet size could indicate a problem with the production and process control system that may affect the quality of the dietary supplement.

(Comment 48) Some comments disagree with the proposed definition of “consumer complaint” because it excluded an adverse event, illness, or injury related to the safety of a particular dietary ingredient. The comments say there should be a consistent approach for handling all complaints, including adverse events. One comment states consumers will not be able to determine whether a product quality issue related to CGMP caused an adverse event. This comment expresses concern that not classifying adverse events as consumer complaints could lead manufacturers to avoid investigating certain adverse events and, therefore, prevent them from determining the appropriate cause and implementing the associated corrective action. The comments stress we should not treat complaints related to CGMP issues differently from other complaints and urged us to classify all adverse events as consumer complaints, whether or not they might have been caused by a particular dietary ingredient.

A few comments state the proposal, which did not specifically address adverse event reporting, but did address the broader category of consumer complaints and would require companies to investigate “adverse event reports,” may simply create more confusion and may contradict the overall objective of a comprehensive adverse event reporting system. The comments also state neither the food CGMP regulations nor the 1997 ANPRM defined “consumer complaints.” The comments say we should delete this definition and deal with consumer complaints separately as part of the new CFSAN Adverse Event Reporting System (CAERS).

One comment states we should define the term “serious adverse dietary supplement experience.” The comment would define a “serious adverse dietary supplement experience” as “any adverse dietary supplement experience occurring at any dose that results in any of the following outcomes:

death, a life-threatening adverse dietary supplement experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse dietary supplement experience and, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.”

(Response) We decline to include in the definition of “product complaint” an adverse event related to the safety of a particular dietary ingredient. The final rule establishes CGMP requirements for dietary supplements and does not focus on whether dietary ingredients that manufacturers may use in their dietary supplements are inherently safe. Nevertheless, we encourage firms to investigate all complaints, regardless of whether the complaints relate to CGMP. Furthermore, mandatory reporting to FDA of serious adverse events is now required as a result of the enactment of the “Dietary Supplement and Non-Prescription Drug Consumer Protection Act” (Public Law 109–462), signed into law on December 22, 2006. In any event, consistent with these CGMP requirements, manufacturers must establish limits on contamination, as needed, for all ingredients or any component they use in manufacturing a dietary supplement.

We agree it may be unclear whether a particular product complaint is related to CGMP. Final § 111.560, relating to product complaints, applies in situations where the product complaint involves a “possible failure of a dietary supplement to meet any of its specifications or any other requirements of this part.” Thus, if a firm is unclear whether a particular complaint it receives

relates to a CGMP issue, we would consider that complaint to be related to a “possible failure” to meet CGMP. Consequently, the firm must comply with the requirements in subpart O, unless the firm affirmatively determines that the complaint is not related to a “possible failure” to meet CGMP, and therefore, is not a “product complaint.” To make this clear, we revised the definition so that it applies to any “communication * * * that could be related to good manufacturing practice” rather than to be any “communication * * * that is related to good manufacturing practice.”

We disagree with comments that suggested that the requirements for product complaints would somehow contradict the overall objective of the CAERS. This final rule has no effect on the mandatory or voluntary reporting of adverse events. We agree some adverse events may be related to a failure to ensure the quality of the dietary supplement as required by the final rule. To the extent that an adverse event is associated with CGMP, it would be considered a “product complaint” under the final rule. The fact that it is considered a product complaint does not mean that such complaint could not be voluntarily reported as an adverse event through CAERS. Such a complaint may be required to be reported under the mandatory reporting requirements of the “Dietary Supplement and Non-Prescription Drug Consumer Protection Act” (Public Law 109–462), signed into law on December 22, 2006. We have added “illness or injury” to the final rule’s definition of “product complaint” as an example of a product problem relating to CGMP to help clarify that there may be some overlap in the type of complaints related to product quality that may also be considered an adverse event.

As for defining “serious adverse dietary supplement experience,” we decline to add such a definition to the final rule. We define certain terms in

a rule to give those terms a clear and consistent meaning. None of the provisions in this rule addresses or even mentions “serious adverse dietary supplement experiences,” so there would be no advantage in codifying a definition for the term in this final rule. If, however, the comment meant to narrow the definition of “consumer complaint” to “serious” illness, or injury, we decline to do so. If a consumer reports an illness or injury, which he or she attributes to consuming a dietary supplement, the report may indicate a problem with the production and process control system for that dietary supplement, even if the injury or illness is not “serious” or severe.

We have, however, decided to delete the last two sentences in the proposed definition of “consumer complaint” (now “product complaint” in the final rule). These sentences explained, in part, that a consumer complaint does not include an adverse event, illness, or injury related to the safety of a particular dietary ingredient independent of whether the product is produced under CGMP. We deleted those sentences because they are unnecessary to include in the definition and can be included as further explanation of what the definition of “product complaint” means in the preamble discussion.

The proposed definition of “consumer complaint” used the phrase “expressing dissatisfaction with the quality of a dietary * * * supplement;” the final rule uses the phrase “expressing concern, for any reason, with the quality of a dietary supplement.” This change is to ensure that even if the consumer is not actually dissatisfied with the product, but has a concern with the product, this is still handled as a product complaint.

We made several editorial or grammatical changes to the definition of product complaint in this final rule for simplicity and revised the order of the listed examples of product complaints. For example, the proposed

definition of “consumer complaint” states the term “means communication that contains any allegation * * *.” The final rule defines “product complaint” as meaning “any communication that contains any allegation * * *.” Another nonsubstantive change was to insert the words “dietary supplements that are” before “superpotent, subpotent” to give the reader a clear understanding as to the article that is superpotent or subpotent.

Finally, we added “electronic” as an example of how a product complaint could be communicated to ensure that all forms of communication are included and added “current” to modify “good manufacturing practice” for consistency.

We discuss in section V of this document, our general response to the comment that stated that neither the food CGMP regulations nor the 1997 ANPRM contains a definition of “consumer complaint,” is in our discussion of whether this final rule exceeds our authority or it has to be identical to the food CGMP regulations. More specifically, we acknowledge that the industry draft that we published in the 1997 ANPRM did not define “consumer complaint.” The industry draft did contain provisions that would be directed to “complaint files.” The provisions for complaint files would require the use of written procedures to handle complaints, retention of records of complaints for a certain time period, and the inclusion of specific information in the record of a complaint.

14. Quality

For purposes solely of this final rule we have decided to define “quality.” Quality means that the dietary supplement consistently meets the established specifications for identity, purity, strength, and composition and limits on contaminants and has been manufactured, packaged, labeled, and held under

conditions to prevent adulteration under section 402(a)(1), (a)(2), (a)(3), and (a)(4) of the act.

(Comment 49) Some comments asked that we define “quality.” Some comments claimed the proposal described “quality” in terms of “identity,” “purity,” and “composition.” One comment would define “quality” as “the total characteristics of a product that bear on its ability to satisfy stated (i.e., labeled) or implied needs of identity, purity, strength and composition.” Another comment would define “quality” as “having the appropriate identity, purity, and strength for the intended purpose.” Another comment would define quality using all the other attributes of identity, purity, strength and composition.

(Response) For purposes only of this final rule, we have added a definition of quality. This definition is not intended to apply to CGMP requirements other than those that apply to dietary supplements. In section III of this document, in the overview discussion, we discuss the concept of “quality” as it applies to these dietary supplement CGMP requirements and the distinction between the use of the term in the final rule and in the proposed rule.

Because we have defined “quality” as encompassing identity, purity, strength, and composition, we have revised each section with requirements for the “identity, purity, quality, strength, and composition” to remove the word “quality.” The affected sections in this final rule are: § 111.3 (definition of batch); § 111.3 (definition of lot); § 111.65 (“What are the requirements for quality control operations?”); § 111.70 (“What specifications must you establish?”); § 111.75 (“What must you do to determine whether specifications are met?”); § 111.80 (“What representative samples must you collect?”); § 111.95 (“Under this subpart E, what records must you make and keep?”);

§ 111.105 (“What must quality control personnel do?”); § 111.455 (“What requirements apply to holding components, dietary supplements, packaging, and labels?”); and § 111.515 (“When must a returned dietary supplement be destroyed, or otherwise suitably disposed of?”).

15. Quality Control

The final rule defines “quality control” as “a planned and systematic operation or procedure for ensuring the quality of a dietary supplement.” The proposed rule defined “quality control” as “a planned or systematic operation for preventing a dietary ingredient or dietary supplement from being adulterated.”

(Comment 50) One comment suggests revising the definition to use more positive language. Specifically, the comment would define “quality control” as “a planned and systematic operation or procedure for ensuring the quality of dietary supplement products.”

(Response) We agree that the comment’s suggested language conveys a positive concept about quality control’s role and value and adopt the language in part. The final rule’s quality control requirements will help ensure compliance with other CGMP requirements and, therefore, will help ensure the quality of the dietary supplement and that the dietary supplement is packaged and labeled as specified in the master manufacturing record. We have defined the term “quality” in this final rule as including preventing a dietary supplement from being adulterated. Consequently, we revised the definition of “quality control” to state that “quality control” means a planned and systematic operation or procedure “for ensuring the quality of a dietary supplement.” We deleted “for preventing a dietary ingredient or dietary

supplement from being adulterated” in the proposed definition since the concept of quality includes preventing adulteration.

16. Quality Control Personnel

The final rule defines “quality control personnel” as “any person, persons, or group, within or outside your organization, who you designate to be responsible for your quality control operations.”

(Comment 51) Some comments seem to suggest that the reference in the 2003 CGMP Proposal to a “quality control unit” mandates a separate unit or department with responsibility for all quality control operations. One comment explains many companies do not have one quality control unit with oversight of all operations within the facility. This comment states companies commonly have each separate section of an operation perform both its function and its own quality control. A few comments would clarify the definition by indicating that a distinct or separate unit need not perform the quality control function. These comments say the quality control function is best performed by a person or persons qualified by training, education, or experience in the different processing areas.

Many comments say we should consider any individual carrying out a quality control function to be part of the quality control unit for purposes of this rule.

(Response) We agree that the quality control function is best performed by a person or persons qualified by training, education, or experience in relevant areas. To the extent that the comments interpreted the proposed definition as requiring firms to have a separate person or group whose sole function in the company is to perform quality control operations or that the quality control functions are limited to those who are employed within the

firm, we disagree. As discussed in the preamble to the proposal, the quality control unit should consist of as many people as necessary to perform the quality control operations (68 FR 12157 at 12252). We have reconsidered the use of the term "unit." In order to clarify that we do not intend to require a separate division or office be created, we instead use the term "personnel." Although we have eliminated references to "unit," we still agree that personnel can be a person, persons, or a group, and as many persons as necessary, who perform the quality control operations. The manufacturer must identify the appropriate person or persons to be responsible for the quality control operations associated with a particular manufacturing operation. For example, the manufacturer may designate one individual as a packaging expert who is responsible for the quality control operations related to packaging, designate a second individual as an expert in deciding whether to accept or reject incoming components, and designate a third individual as an expert in deciding whether in-process specifications are met at certain control points. The definition does not limit the other activities that these designated individuals may perform within the manufacturing operations; thus, for example, the packaging expert who performs the quality control function for packaged dietary supplements could also have responsibilities in the actual packaging operation. Quality control responsibilities and specific activities are distinct and separate from any other responsibilities and specific activities that an employee might perform for any other operation. In addition, the quality control operations may be performed by someone outside the organization (such as a contractor).

To clarify these points and to prevent potential misinterpretation of quality control operations, we revised the definition of "quality control unit." Instead

of a unit, quality control personnel who perform quality control operations may be a person, persons, or group and may be “within or outside of your organization.” We also added a new § 111.12(b) to require you to identify who is responsible for your quality control operations. Under final § 111.12(b) each person who is identified to perform quality control operations must be qualified to do so and have distinct and separate responsibilities related to performing such operations from those responsibilities that the person otherwise has when not performing such operations. Throughout the codified, we use the term “quality control personnel” when referring to the performance of specific quality control operations. The term “quality control personnel” refers to the person or persons designated to perform the particular quality control operation.

17. Representative Sample

The final rule defines “representative sample” as “a sample that consists of an adequate number of units that are drawn based on rational criteria, such as random sampling, and that are intended to ensure that the sample accurately portrays the material being sampled.” This definition is similar to the proposed definition of “representative sample.” We have added “an adequate” before “number” to emphasize that the sample must be sufficient for its purpose. We also made nonsubstantive grammatical changes to insert “that are” between “and” and “intended.”

(Comment 52) Some comments note the proposed rule would use the terms “representative sample,” “reserve sample,” and “representative reserve sample” but would only define “representative sample.” The comments ask us to clarify the distinction, if any, between these terms.

(Response) A “reserve sample” is a sample that is to be held or kept for a designated time. It differs from a “representative sample” in the sense that a representative sample is not always kept; for example, one might take a representative sample to test product quality, but one would not necessarily keep every tested sample.

To clarify this distinction, the final rule now defines a “reserve sample” as “a representative sample of product that is held for a designated period of time.” We also revised the rule to refer solely to a “reserve sample” rather than use both “reserve sample” and “representative reserve sample.”

18. Reprocessing

The final rule defines “reprocessing” as “using, in the manufacture of a dietary supplement, clean, uncontaminated components or dietary supplements that have been previously removed from manufacturing and that have been made suitable for use in the manufacture of a dietary supplement.” We modified the definition that, in part, read “* * * dietary supplements that have been previously removed from manufacturing for reasons other than insanitary conditions” by removing “for reasons other than insanitary conditions” to expand the scope of what may be reprocessed. We explain the reason for the latter change in our response to the following comments. We also changed “unadulterated” to “uncontaminated” to be consistent with the revisions we have made in other sections, including the definition of quality.

(Comment 53) Some comments ask us to clarify whether components or dietary supplements that have been successfully treated to reduce microbial levels to acceptable levels can be reprocessed. Some comments object to the proposed definition of “reprocessing” because it did not include components or dietary supplements removed for insanitary conditions, and several

comments object to the restrictions to reprocessing described in proposed §§ 111.35(i)(4)(iii) and 111.50(f), because, they argue, the definition and sections associated with reprocessing would not permit the reprocessing of previously insanitary ingredients even if there are processes available that are safe and effective in removing foreign matter, microorganisms, or chemicals that may have rendered the ingredient “insanitary.” One comment would revise the definition as follows: “Reprocessing means using, in the manufacture of a dietary supplement, clean, unadulterated components * * * or dietary supplements that have been previously removed from manufacturing for reasons other than insanitary conditions or that have been successfully reconditioned so that they are suitable for use.”

(Response) We agree that materials can be treated, subjected to in-process adjustments, or reprocessed when there are suitable processes available, and we revised the definition of “reprocessing” to reflect this. However, there must be appropriate oversight of the treatment, in-process adjustments, and reprocessing so the dietary supplement will still meet required specifications. Therefore, we added a conforming requirement to final §§ 111.90(b) and 111.140(b)(3)(vi) to require oversight by quality control personnel for any reprocessing, treatment, or in-process adjustment of a dietary supplement that have been previously removed from manufacturing and that have been made suitable for use in the manufacture of a dietary supplement (see sections X and XI of this document).

19. Reserve Sample

The final rule contains a new definition of “reserve sample.” “Reserve sample” is defined as “a representative sample of product that is held for a

designated period of time.” We explain our reasons for creating this definition in this section under the definition of “representative sample.”

20. Sanitize

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

The final rule’s definition of “sanitize” differs from the proposal in that the proposed definition would have specified a reduction of 5 logs or 99.999 percent reduction of “representative disease microorganisms of public health significance” and “other undesirable microorganisms” and would have specified the use of heat or chemicals. The preamble to the 2003 CGMP Proposal explained that we based the proposed definition of “sanitize” on the definition of “sanitization” in the “Food Code” (which is a model that gives food control authorities a scientifically sound technical and legal basis for regulating the retail and food service segment of the industry) because dietary supplements are often consumed without further processing, similar to foods consumed in retail outlets (68 FR 12157 at 12179). The preamble to the 2003 CGMP Proposal also explained that, to achieve the reduction levels in the proposed definition, one would need to validate control measures to ensure they are both appropriate to their operation and scientifically sound. The preamble explained that in many cases, manufacturers may rely on a written certification from the equipment manufacturer or may obtain a written scientific evaluation of a process, especially in cases where two or more control

measures are used to accomplish the 99.999 percent reduction in the target pathogen, to ensure the process is adequate to destroy microorganisms of public health significance or to prevent their growth.

(Comment 54) Many comments object to the proposed text concerning the application of heat or chemicals to a food contact surface to yield a reduction of 5 logs or 99.999 percent of representative disease organisms of public health significance. The comments state the aspect of the proposed definition is overly prescriptive, beyond our legal authority, and would not provide additional public health benefits. Many comments say it is inappropriate to use the definition of sanitization from our Food Code because retail and manufacturing operations are distinct. A few comments assert the process of manufacturing dietary supplements shares more in common with food or drug manufacturing than with retail operations. Most comments recommend that we define "sanitize" in the manner that was presented in the 1997 ANPRM and consistent with the current food CGMP definition at § 110.3 so that "sanitize" means "to adequately treat dietary product contact surfaces by a process that is effective in destroying vegetative cells of microorganisms of public health significance, and in substantially reducing numbers of other undesirable microorganisms, but without adversely affecting the product or its safety for the consumer."

One comment states that consistently validating the effectiveness of the sanitizing procedure is impractical and recommended we state instead that equipment, utensils, etc., should be cleaned and sanitized in a manner that keeps undesirable microorganisms and other adulterants from contaminating all components, ingredients, in-process materials, and finished product. The comment claims that, by this approach, the microbial and analytical test results

of product produced on a facility's equipment, coupled with random testing of final rinse water after cleaning and sanitizing equipment and utensils, would provide sufficient and continuous evidence of a proper and effective cleaning and sanitizing plan.

Two comments claim that the proposed definition for sanitize denotes "validation methodology" found in drug CGMP, and that we must base dietary supplement CGMP on food rather than on drug standards.

Other comments express concern about validating control measures to ensure that they are scientifically sound and appropriate to operations and the economic burden to do the testing. A few comments state it would be difficult to show a 100,000-fold reduction on an already cleaned surface, particularly if the pre-sanitization level is at or near the lower limit of the test method employed.

One comment states the definition required the manufacturer to demonstrate a 100,000-fold reduction in microbial count every time a food contact surface is sanitized. A few comments express concern that processing lines would have to be closed down each time they are sanitized in order to test them, creating a financial hardship especially on smaller operations. Other comments ask us to give companies the flexibility necessary to monitor sanitation needs based on individual products and manufacturing operations to be consistent with existing industry practices and food and drug CGMPs.

One comment requests we clarify that a sanitizing agent for use on food processing equipment must be approved in accordance with part 178, *Indirect Food Additives: Adjuvants, Production Aids, and Sanitizers* (21 CFR part 178) and our expectations with respect to what documentation would be necessary to prove the effectiveness of the sanitizer used. Two comments say the

proposed definition of sanitize means that manufacturers must perform validation studies to demonstrate that the sanitizers they are using reduce the microbial load on equipment by 100,000-fold, a requirement for a “sanitizer” under regulations issued by the Environmental Protection Agency. The comments say a sanitizer should not be held to this standard for the purpose of reducing microbial loads on food product contact surfaces, and that manufacturers of a solid dosage form may not need to “sanitize” their equipment because the processing environment is not suitable for microbial growth due to the low water activity. One comment recommended using the approach in the Food Code, which specifies conditions under which chemical sanitizers listed in § 178.1010 may be used, including the requirement that they be used in accordance with the Environmental Protection Agency-approved manufacturer’s label use instructions, and be used for dietary supplements rather than imposing a validation requirement on manufacturers.

Some comments would divide the definition of “sanitize” by creating separate definitions for “sanitize” and “sanitizing agent.” The comments would define “sanitize” as meaning “to adequately treat equipment, containers, utensils, or any other dietary product contact surface by applying a sanitizing agent on cleaned food contact surfaces.” One comment would define “sanitizing agent” as “cumulative heat or chemicals that, when evaluated for efficacy, yield a reduction of 5 logs, which is equal to 99.999 percent reduction, of representative disease microorganisms of public health significance and substantially reduce the numbers of other undesirable microorganisms, but without adversely affecting the product or its safety for the consumer.” Another comment would define “sanitizing agent” in a similar manner, except it would omit references to a 5-log reduction.

(Response) The proposed definition of “sanitize” was intended to give firms the flexibility to monitor sanitation needs based on their products and operations. We did not intend to suggest that manufacturers had to demonstrate a 100,000-fold reduction in microbial count every time they sanitized a contact surface, nor did we intend, as some comments claimed, to have firms close down processing lines every time they were sanitized to test them for microbial reduction. Rather, the language of the proposed rule was intended to make it clear that processes used to sanitize contact surfaces should be effective. However, we recognize that the proposed definition caused confusion as to our intent. The proposed definition may have been interpreted as proposing validation to ensure an area was sanitized; however our intent was simply to require that effective sanitizers and sanitizing processes be used, just as in food establishments. Therefore, in order to clarify the provision, we have revised the definition of “sanitize” to be consistent with § 110.3(o). The final rule defines “sanitize” as adequately treating “cleaned equipment, containers, utensils, or any other cleaned contact surface by a process that is effective in destroying vegetative cells of microorganisms of public health significance, and in substantially reducing numbers of other microorganisms, but without adversely affecting the product or its safety for the consumer.” The final definition of sanitize does not include any statements about mechanisms that you may use to achieve compliance because including such nonbinding information is inconsistent with our current practices for establishing regulations.

We note that the Environmental Protection Agency has regulatory authority over certain uses of sanitizers as pesticide chemicals and we have regulatory authority over certain uses of sanitizers as food additives. Under

section 201(q)(1)(B) of the act, as amended by the Food Quality Protection Act (FQPA) (Public Law 104–170) and the Antimicrobial Regulation Technical Corrections Act (ARTCA) (Public Law 105–324), certain substances used as food contact surface sanitizing solutions are subject to the Environmental Protection Agency’s regulatory authority as pesticide chemicals. The Environmental Protection Agency recently codified tolerance exemptions under section 408 of the act (21 U.S.C. 346a) for those food contact surface sanitizing solutions that were previously subject to our authority at § 178.1010 and transferred to the Environmental Protection Agency’s authority under FQPA and ARTCA (see 40 CFR 180.940 (69 FR 23113, April 28, 2004). Such pesticide chemicals must comply with the Pesticide Tolerance regulations in 40 CFR 180.940. Sanitizers used on food packaging must comply with our regulations at § 178.1010. For an in depth discussion of appropriate sanitizers for food contact surface use, see the Environmental Protection Agency’s *Pesticides; Tolerance Exemptions for Active and Inert Ingredients for Use in Antimicrobial Formulations (Food Contact Surface Sanitizing Solutions)* (69 FR 23113, April 28, 2004) and *DIS/TSS–4 Efficacy Data Requirements Sanitizing Rinses (for previously cleaned food-contact surfaces)* (January 30, 1979) (Ref. 27) (available on the Internet at http://www.epa.gov/oppad001/dis_tss_docs/dis-04.htm).

21. Theoretical Yield

The final rule defines “theoretical yield” as “the quantity that would be produced at any appropriate step of manufacture or packaging of a particular dietary supplement, based upon the quantity of components or packaging to be used, in the absence of any loss or error in actual production.”

We received no substantive comments on the proposed definition.

22. Water Activity

The final rule defines “water activity” as “a measure of the free moisture in a component or dietary supplement and is the quotient of the water vapor pressure of the substance divided by the vapor pressure of pure water at the same temperature.”

We received no substantive comments on the proposed definition.

23. We

The final rule explains that “we” means the United States Food and Drug Administration.

The final rule’s definition is identical to the proposed definition. We received no substantive comments on the proposed definition.

24. You

The final rule defines “you” as a “person who manufactures, packages, labels, or holds dietary supplements.”

25. What Other Terms Did the Comments Want Defined?

(Comment 55) Some comments ask us to define “adulteration” (based on the provisions of section 402 of the act), “dietary ingredient,” and “dietary supplement” (based on the definition in section 201(ff) of the act).

(Response) We decline to revise the rule as suggested by the comments. The terms have meaning within the context of the act and case law. Further, under final § 111.3 the act’s definitions and interpretations “apply to such terms when used in this part.” Thus, there is no need for us to define the terms as requested by the comments.

(Comment 56) Proposed § 111.35(e)(2) would require a person to establish a specification for any point, step, or stage in the manufacturing process where

control is necessary to prevent adulteration, and proposed § 111.35(f) would require monitoring of the in-process control points, steps, or stages to ensure these established specifications are met and to detect any unanticipated occurrence that may result in adulteration. Some comments ask us to define the term “control point” as “any point, step or stage in the manufacturing process where control is necessary to prevent adulteration.”

(Response) We decline to add a definition of “control point” as requested by the comments. Instead, we revised final § 111.75(b) (formerly proposed § 111.35(f)) to state that you must monitor the in-process points, steps, or stages where control is necessary to ensure the quality of the finished batch of dietary supplement; this revision eliminates the need to define “control point.”

(Comment 57) Several comments would have us define one or more of the following terms: Identity, purity, strength, and composition. Some comments suggest specific text for the definitions.

Similarly, some comments suggest codifying the preamble description that we used for these terms, i.e., the phrase “identity, purity, quality, strength, and composition” means that the production on a batch-by-batch basis is consistent with the master manufacturing record and is what it is represented on the label to be (identity); is without impurities and is the desired product (purity); is the identity, purity, and strength for its intended purpose (quality); is the concentration, that is, the amount per unit of use intended (strength); and is the intended mix of product and product-related substances (composition) (68 FR 12157 at 12176). One comment says “identity” should mean “a substance or product is what it is represented on the label to be.”

One comment says that it does not seem appropriate to define the term “purity” to mean “without impurities.” The comment states it would be

difficult to consider an herbal extract as being “pure” because it is a mixture of naturally occurring compounds in a solvent. Another comment suggests the term “purity” be defined to mean “free from objectionable and/or deleterious levels of impurities including, but not limited to, heavy metals, pesticides, mycotoxins, radioactivity, filth, extraneous material, molds, yeasts and bacteria.” Another comment suggests defining the term “purity” as “having the intended identity and composition and being without significant impurities.” However, the comment does not explain what is meant by “without significant impurities.”

One comment suggests defining the term “strength” as “having the intended concentration, that is, the amount of the dietary ingredient per unit of use (tablet, capsule, soft gel, teaspoon, or other unit).” Another comment expresses concern about the use of the term “strength” in relationship to nonstandardized herbals because there are no current industry standards for these products. This comment suggests we clarify the term “strength” so it refers to having the correct amount of a stated ingredient. One comment notes St. Johns wort has a composition of approximately 40 different constituents in addition to the essential oil that contains numerous constituents. The comment asks which constituent it should use to determine “strength.” Another comment would use the term “quantity” instead of “strength.”

One comment would define “composition” as “having the intended mix of components or ingredients, including dietary ingredients.” Another comment would delete “composition” from the rule because, the comment claimed, an FDA investigator might conclude that “composition” refers to every constituent of every botanical. According to this comment, there are many tests that could be used to identify the botanical constituents, but that

it would be economically exhausting considering the number of botanical constituents, and it would not contribute to quality or safety.

(Response) We decline to revise the rule to define identity, purity, strength, or composition. The exact way in which the dietary supplement industry uses these terms may vary, and defining these terms could limit the flexibility that is needed to accommodate such variations.

Nevertheless, to elaborate on our interpretation of identity, purity, strength, and composition, and to respond to the particular concerns raised by some comments, we provide the following information.

a. *Identity.* The “identity” of a dietary supplement refers to the dietary supplement’s consistency with the master manufacturing record and/or that it is the same as described in the master manufacturing record.

b. *Purity.* The “purity” of a dietary supplement refers to that portion or percentage of a dietary supplement that represents the intended product. For example, amino acids generally can exist in two forms (i.e., dextro (D-, or right) and levo (L-, or left) forms) called enantiomers. Enantiomers have the same chemical formula and the same chemical structure, but differ in their three-dimensional orientation. If you manufacture a dietary supplement to provide the amino acid L-arginine, and you determine that 90 percent of the manufactured product is L-arginine and 10 percent of the manufactured product is D-arginine, you could describe your L-arginine product as “90 percent pure.” As another example, if you manufacture a mixture of triglycerides that provides polyunsaturated fatty acids in the diet, the manufactured triglycerides may contain small amounts of free fatty acids and sterols. The free fatty acids and sterols could derive, for example, from the source of the triglycerides or could be byproducts of the manufacturing

process. If you determine that 95 percent of the manufactured product is the mixture of the triglycerides that provides the polyunsaturated fatty acids, and 5 percent of the product is free fatty acids and sterols, you could describe the purity of your product as "95 percent pure."

Just as we use the term "purity" to refer to the identity and amount of a dietary supplement that is the desired product, we use "impurity" to refer to the identity and amount of a dietary supplement that is not the desired product. In the previous examples, we view the D-arginine that is present in the product that is intended to be L-arginine as an "impurity," and we view the free fatty acids and sterols that are present in the product that is intended to be a mixture of triglycerides that provide polyunsaturated fatty acids in the diet as "impurities." For the purposes of these examples, we do not view these "impurities" as "contaminants."

If the comments were concerned that the dietary supplement CGMP requirements regarding a dietary supplement's "purity" mean that we expect you to characterize each constituent of a natural product to determine whether each constituent is present in a certain pre-established quantity (i.e., purity specification) to determine whether it contributes to the "purity" of the dietary supplement or would be considered as an "impurity," we do not consider such constituents to be "components" of a dietary supplement (see discussion of the definition of component in this section). For example, if you manufacture a dietary supplement containing fish oil, we would not consider the triglycerides, which are constituents of the fish oil, to be components. Likewise, we would not consider particular fatty acids (such as the polyunsaturated fatty acids docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA)), which are constituents of the triglycerides, to be components of