Status: Currently Official on 12-Feb-2025
Official Date: Official as of 01-Aug-2021
Document Type: General Chapter
DocId: GUID-B1EB10D3-6473-4AC9-99B7-4AD444683A01_2_en-US
DOI: https://doi.org/10.31003/USPNF_M99987_02_01
DOI Ref: 0pf8r

⟨2750⟩ MANUFACTURING PRACTICES FOR DIETARY SUPPLEMENTS

Change to read:

▲GENERAL PROVISIONS

The aim of this chapter is to establish requirements that address the specific regulatory obligations of the dietary supplement industry and the additional requirements necessary to achieve compliance with the *USP–NF* quality specifications. The chapter covers the process, facilities, and controls to be used in the manufacturing, packaging, labeling, holding, and distributing of dietary supplements consistent with the FDA current good manufacturing practices (cGMP) regulations in title 21, part 111 of the *Code of Federal Regulations* in order to help dietary supplement manufacturers ensure that dietary supplements are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the product specification according to USP standards.

A manufacturing and in-process control system must be designed and implemented to cover all stages of manufacturing, packaging, labeling, holding, and distribution of the dietary supplement to ensure the quality of the dietary supplement and its proper packaging and labeling as specified in the master manufacturing and packaging control records.

An overall scheme of quality systems adopted in the chapter consists of the following:

1. *Quality management system*—This system assures overall compliance with cGMPs and internal procedures and specifications. This system includes the quality control unit and all of its review and approval duties (e.g., change control, reprocessing, batch release, annual record review, validation protocols, and reports, etc.). It includes all product defect evaluations and evaluation of returned and salvaged products. The quality management system must define the quality unit obligations and authorities to ensure that all material use and disposition decisions are independent of any conflict of interest.
2. *Physical plant and equipment system*—This system includes the measures and activities which provide an appropriate physical environment and resources used in the production of the finished products. It includes buildings and facilities along with maintenance; equipment qualifications, calibration, and preventative maintenance; utilities that are not intended to be incorporated into the product such as heating, ventilation, and air-conditioning (HVAC), compressed gases, steam and water systems. The water systems refer to both the “equipment system” and the “material system”.
3. *Materials management system*—This system includes measures and activities to control finished products; components, including water or gases that are incorporated into the product; and containers and closures. It includes validation of computerized inventory control processes, product storage, distribution controls, and records.
4. *Production operations and controls system*—This system includes measures and activities to control the manufacture of finished products, including batch compounding, dosage form production, in-process sampling and testing, and process validation.
5. *Packaging and labeling operations and controls system*—This system includes measures and activities that control the packaging and labeling of finished products. It includes written procedures, label examination and usage, label storage and issuance, packaging and labeling operations controls, and validation of these operations.
6. *Laboratory control system*—This system includes measures and activities related to laboratory procedures, testing, analytical methods development and validation or verification, and the stability program.

Warehouses or other storage facilities for a retailer as well as warehouses or other storage facilities that sell directly to individual consumers must comply with the requirements pertaining to holding dietary supplements. The requirements pertaining to holding dietary supplements do not apply to holding those dietary supplements at a retail establishment for the sole purpose of direct retail sale to individual consumers.

The following is a chapter outline:

1. QUALITY MANAGEMENT

1.1 General Principles

Quality unit operations must be implemented in manufacturing, packaging, labeling, laboratory, and holding operations for the production of dietary supplements to ensure the quality of the supplements and their packaging and labeling is in accordance with the specifications.

Quality should be the responsibility of all persons involved in manufacturing, testing, packaging, labeling, and holding dietary supplements. An effective system for managing quality that involves the active participation of management and appropriate manufacturing personnel must be established, documented, and followed. Management oversight of quality should encompass the organizational structure, procedures, processes, resources, and activities necessary to ensure that the dietary supplement will meet its intended specifications for quality. All quality-related activities must be defined and documented.

There must be a quality unit(s) that is independent of production (and any other conflicts of interest) and that fulfills both quality assurance (QA) and quality control (QC) responsibilities. This can be in the form of separate QA and QC units or a single individual or group, depending on the size and structure of the organization.

All quality- and manufacturing-related activities must be recorded and reviewed contemporaneously, signed, and dated.

1.2 Organization and Personnel

1.2.1 General

Written procedures must be established and followed for creating and maintaining job position descriptions and listing job responsibilities and required qualifications for education, training, and experience. There must be an organizational chart clearly delineating the structure of the organization and the relationships and relative ranks of its parts and job positions.

1.2.2 Responsibilities of the Quality Unit(s)

A quality unit involved in all quality related matters must be established, which must review all appropriate quality related documents. Quality unit personnel must ensure that manufacturing, packaging, labeling, and holding operations ensure the quality of the dietary supplement and that the dietary supplement is packaged and labeled in accordance with the specifications.

The primary responsibilities of the independent quality unit(s) should not be delegated, and these responsibilities shall be described in writing. The quality unit(s) shall have the primary responsibility and authority for the following:

- Approving the release or rejection of (i.e., making a disposition decision for) all dietary supplements for distribution or in-process materials for use outside the control of the manufacturer;
- Establishing a system to approve the release or rejection of components, in-process materials, packaging materials, and labeling materials;
- Reviewing and approving the release or rejection of products manufactured, packaged, labeled, or held under contract by another company;
- Reviewing and approving all specifications;
- Reviewing and approving all master production, packaging, and labeling instructions;
- Reviewing and approving all procedures impacting the quality of in-process materials and dietary supplements;
- Reviewing completed production records to ensure that no errors have occurred or, if errors have occurred, that they have been investigated and resolved;
- Ensuring that all deviations are properly documented and that critical deviations are investigated and resolved;
- Ensuring that internal audits (self-inspections) are performed;
- Ensuring that corrective and preventative actions as a result of investigations (deviations and complaints) and internal audits are implemented in a timely manner;
- Establishing a system to evaluate and approve suppliers of components, packaging materials, and labeling as well as suppliers of manufacturing and laboratory services (i.e., contract manufacturers and contract laboratories);
- Establishing a system to evaluate and approve changes that potentially impact the quality of dietary supplements;
- Reviewing and approving test method validation protocols and reports;
- Establishing a system to handle complaints and ensure that quality-related complaints are investigated and resolved;
- Establishing effective systems for maintaining and calibrating equipment and instruments;
- Ensuring that materials are properly tested and the results are reported;
- Ensuring that there is stability data to support the shelf-life or expiry date and labeled storage conditions of dietary supplements;
- Performing product quality reviews and trend analysis, as needed;
- Reviewing and approving cGMP training documentations and ensuring the maintenance of these records.

The quality control unit (i.e., quality control laboratory) must have the responsibility for approving or rejecting all laboratory processes procedures, specifications, controls, tests, examinations, and deviations (planned and unplanned) from or modifications to them, that may affect the identity, strength, quality, and purity of the dietary supplement. All responsibilities and procedures applicable to the quality control unit must be in writing.

The quality unit personnel must be identified and qualified to perform quality assurance and/or quality control operations. Any other responsibility that such personnel may have within the company must not interfere or conflict with the ability to make independent judgments about quality.

The designated quality control personnel who conducts a material review and makes the disposition decision must, at the time of performance, document the material review and disposition decision made.

1.2.3 RESPONSIBILITIES FOR PRODUCTION OPERATIONS

The responsibilities for production operations must be documented in writing and should include the following:

- Preparing, reviewing, approving, and distributing the instructions for the production of in-process materials and dietary supplements according to written procedures;
- Reviewing all production batch records and ensuring that they are completed and signed;
- Ensuring that production facilities are clean and sanitized, if needed;
- Ensuring that the premises and equipment are maintained and records kept;
- Ensuring that HVAC, dust collection, and other systems are appropriately designed to minimize the potential for cross-contamination;
- Ensuring that, when appropriate, physical and spatial separation are used in combination to minimize the potential for cross-contamination and to prevent mix-ups;
- Ensuring that manufacturing verification/validation protocols and reports are reviewed and approved, if available;
- Evaluating proposed changes in product, process, or equipment; and
- Ensuring that new and any modified facilities and equipment are qualified through an appropriate documented change control system.

1.2.4 PERSONNEL QUALIFICATIONS

Each person engaged in the manufacture of dietary supplements should have the proper education, training, and experience (or any combination thereof) needed to perform the assigned functions. Training should be in the particular operation(s) that the employee performs as they relate to the employee's functions.

Each person responsible for supervising the manufacture of dietary supplements must have the proper education, training, and experience (or any combination thereof) to perform assigned functions in such a manner as to provide assurance that the dietary supplement has the safety, identity, strength, quality, and purity that it is represented to possess.

An adequate number of qualified personnel to perform and supervise the manufacture of dietary supplements should be provided.

Personnel qualifications apply equally to contractors, consultants, and temporary employees. Records should be maintained stating the name, address, qualifications, and type of service provided by contractors and consultants.

1.2.5 PERSONNEL TRAINING

Training should be regularly conducted by qualified persons and should cover, at minimum, the particular operations that the employee performs and current good manufacturing practice (GMP) as it relates to the employee's functions. Training requirements should be specified, e.g., read and understand, instructional with trainer, on-the-job training. Training should be periodically assessed by reviewing and approving GMP training documentation and ensuring that these records are maintained. Appropriate documentation of training must be retained by the company, including date of training, the type of training, name of trainer if applicable, the person(s) trained, and any assessment results (e.g., test results).

1.2.6 PERSONNEL RESPONSIBILITIES

The company management must take all reasonable measures and precautions to ensure the following:

1.2.6.1 Preventing microbial contamination: Any person who, by medical examination, by the person's self acknowledgment, or supervisory observation, is shown to have, or appears to have an illness (including a fever, coughing, and sneezing), infection, open lesion, or any other abnormal source of microbial contamination that could result in microbial contamination of components, in-process material, dietary supplements, or contact surfaces must be excluded from working in any operations that may result in such contamination until the aforementioned conditions no longer exist, or unless conditions such as open lesions, boils, and infected wounds are adequately covered (e.g., by an impermeable cover). Personnel must be instructed to report such conditions to their supervisors.

1.2.6.2 Hygienic practices: All persons working in an operation during which adulteration of components, in-process material, dietary supplements, or contact surfaces could occur must use hygienic practices to the extent necessary to protect against such adulteration. These practices include the following:

- Wearing outer garments in a manner that protects against the contamination of components, in-process material, or dietary supplements, or any contact surface;
- Maintaining adequate personal cleanliness;
- Removing cosmetics from parts of the body that may contact components, in-process materials, dietary supplements, or contact surfaces;
- Washing hands thoroughly (and sanitizing if necessary to protect against allergen cross-contact and contamination with microorganisms) in an adequate hand-washing facility before starting work, and at any other time when the hands may have become soiled or contaminated;
- Removing all unsecured jewelry and other objects that might fall into components, in-process materials, dietary supplements, equipment, or packaging materials, and removing hand jewelry that cannot be adequately sanitized during periods in which components, in-process materials, or dietary supplements are manipulated by hand. If hand jewelry and cosmetics cannot be removed, they must be covered by material that is maintained in an intact, clean, and sanitary condition and that effectively protects against contamination of components, in-process materials, dietary supplements, or contact surfaces;
- Maintaining gloves used in handling components, in-process materials, or dietary supplements in an intact, clean, and sanitary condition. The gloves must be of impermeable material;
- Wearing face masks when working within the production and packaging areas;

- Wearing where appropriate, in an effective manner, hair nets, caps, beard covers, or other effective hair restraints;
- Storing clothing or other personal belongings in areas other than where components, in-process materials, dietary supplements, or any contact surface are exposed, where contact surfaces are washed, or where clean work uniforms and gowning are stored;
- Maintaining footwear protocol when working within the production and packaging areas;
- Not eating food, chewing gum, drinking beverages, or using tobacco products in GMP or critical areas where components, in-process materials, dietary supplements, or contact surfaces are exposed or where contact surfaces are washed; and
- Taking any other precautions necessary to protect against allergen cross-contact and contamination of components, in-process materials, dietary supplements, or contact surfaces with microorganisms, allergens, filth, foreign substances, or other extraneous materials, including perspiration, hair, cosmetics, tobacco, chemicals, and medicines applied to the skin. This may include restricting the movement of individuals working in unit operations with known allergens so that those individuals are not allowed to move into non-allergen production areas, and/or color coding of in-process allergen-containing materials to differentiate from non-allergen-containing materials.

1.3 Documentation and Records

1.3.1 GENERAL

Clear, complete, accurate records for all operations and procedures should be documented appropriately. [NOTE—see *Good Documentation Guidelines* ⟨1029⟩ for recommendations about appropriate documentation practices.]

All documents related to the manufacture of dietary supplements must be initiated, prepared, reviewed, approved, distributed, and archived according to written procedures. Such documents can be in paper or electronic form. If the firm chooses to maintain its documentation electronically, the resulting documents and related records must be 21 CFR Part 11 compliant.

When entries are made in records, these must be made legibly and indelibly in spaces provided for such entries, directly after performing the activities, and should identify the person making the entry, and the day, and time as needed, when the entry was made. All dates must include day, month, and year in a consistent format. Numerical results must have appropriate numerical units, and calculations must be made with appropriate rounding and significant figures. Corrections to entries must be dated and signed, leaving the original entry still legible. If the reason for the correction is not obvious (e.g., date transcription error), then a statement should be made to provide clarity on the correction.

1.3.2 CONTROL OF DOCUMENTATION

The issuance and revision, superseding and withdrawal of all documents must be controlled with maintenance of revision histories. A procedure should be established for retaining all appropriate documentation (e.g., procedures and records). There should be proper control over:

- Standard operating procedures (SOPs) and work instructions;
- Forms: content, revision, review; each form must be associated with one or more SOPs and correspondingly numbered/versioned/dated;
- Master manufacturing records;
- Laboratory testing method;
- Spreadsheets: spreadsheet for specific project—accuracy checked by reviewer, spreadsheet for routine use—validated, access/revision controlled;
- External documents: proprietary documents, guidance documents issued by outside agency;
- Uncontrolled documents;
- For reference only documents;
- Employee notes and memos.

A formal documentation filing system (physical or electronic) should be established, with appropriate security.

1.3.3 RECORDS RETENTION

The retention periods for these documents must be specified. Written records must be kept, at minimum, for one (1) year past the shelf life date of the dietary supplement associated with those records. Records must be kept as original records, as true copies (such as photocopies, microfilm, compact disk, or other accurate reproductions of the original records), or as electronic copies. All electronic records must comply with 21 CFR Part 11—*Electronic Records; Electronic Signatures*.

Serious adverse event reports must be kept, at minimum, for six (6) years from the date the report is received by the responsible party.

All records or copies of records required under this general chapter must be readily available during the retention period for inspection by the FDA when requested. If encryption or data reduction techniques are used, suitable equipment to retrieve the information must be made readily available to the FDA.

1.4 Change Control

A formal change control system must be established to evaluate all changes that may affect the production and quality of dietary supplements. Written procedures should provide for the identification, documentation, appropriate review, and approval of changes to components, packaging materials, labeling, material specifications, analytical procedures, facilities, utility systems, equipment, computer systems, production operations, and packaging and labeling operations.

Any proposals for GMP relevant changes should be drafted, reviewed, and approved by the appropriate approved units, and reviewed and approved by the quality unit(s).

The potential impact of the proposed change on the quality of the dietary supplement should be evaluated. A change classification system based on the nature and extent of the change (e.g., major, minor) and its impact on the process (e.g., critical, non-critical) should be established with clear definitions. This classification system should be used to determine the level of testing, validation, and documentation needed to justify changes to a system or process. When implementing approved changes, measures should be taken to ensure that all documents affected by the change are revised.

The potential for changes to affect established expiry dates (e.g., changes to product formulation) should be evaluated. If necessary, the dietary supplement produced by the change can be placed on an accelerated stability program and/or added to the stability monitoring program.

Manufactures should require their contract manufactures or packagers to notify them of changes from established production process controls that can affect the quality of the dietary supplement.

1.5 Deviations and Material Reviews

1.5.1 DEVIATIONS

Written procedures must be established and followed for documenting all deviations, and for investigating critical deviations. Any deviation from established procedures and standards should be documented and explained. Critical deviations should be investigated, and the investigation and its conclusions should be documented. The investigation should extend to any and all batches of material that may have been associated with the specific failure or deviation. The quality unit must ensure that critical deviations are investigated and resolved. Corrective and preventative actions should be implemented and verified in a timely manner.

1.5.2 MATERIAL REVIEW

Written procedures must be established and followed for conducting material reviews and making disposition decisions, and for the quality unit to approve or reject any treatment or in-process adjustment of a component that is rejected, or reprocessing of a dietary supplement that is rejected.

Quality unit personnel must conduct all required material reviews and make all required disposition decisions. Quality unit personnel must conduct a material review and make a disposition decision if:

- A specification is not met for a component, in-process material, packaging, labeling, dietary supplement, a dietary supplement received for packaging and labeling, or finished packaged and labeled dietary supplement;
- A batch record that deviates from the master manufacturing record, including when any step is not completed, and any deviation from the instructions contained therein;
- There is any unanticipated occurrence during manufacturing operations that adulterates or may lead to adulteration and/or misbranding of the component, dietary supplement, or packaging, or could lead to the use of a label not specified in the master manufacturing record;
- Calibration of an instrument or control suggests a problem that may have resulted in a failure to ensure the quality of a batch or batches of a dietary supplement;
- A dietary supplement is returned.

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

When an established specification is not met, quality unit personnel must reject the component, in-process material, dietary supplement, packaging, or labeling, unless quality unit personnel approve a treatment, an in-process adjustment, or reprocessing, that will ensure the quality of the finished dietary supplement and that the dietary supplement is packaged and labeled as required in the master manufacturing record.

The quality unit personnel and each qualified individual who provides information relevant to the material review and disposition decision and subsequent approval or rejection of the treatment, in-process adjustment, or reprocessing of the subject material must document performance of the review, by signing and dating in the deviation investigation and material review report at the time of performance.

Deviation investigation and material review reports must include:

- Description of the specific deviation or unanticipated occurrence;
- Description of the root cause investigation;
- Evaluation of whether or not the deviation or unanticipated occurrence has resulted in or could lead to a failure to ensure the quality of the dietary supplement or failure to package and label the dietary supplement as specified in the master manufacturing record;
- Identification of corrective action(s) and preventive action(s) taken with timelines;
- Description of any material reviews, and a scientifically valid reason for any treatment or in-process adjustment of a component or in-process material that is rejected, or any reprocessing of a dietary supplement that is rejected, so as to correct the applicable deviation or unanticipated occurrence, along with the quality unit personnel's approval signature and date, when performed;
- Conclusion(s), including the explanation of the final disposition decision (approval or rejection) made for the subject article; and
- Signatures of individual(s) designated to perform quality unit operations, who conducted the material review and made the disposition decision, and of each qualified individual who provides information relevant to that material review and disposition

decision.

Documentation of any material review and disposition decision, or reference to the deviation investigation and material review report, must be included in the appropriate batch production record.

1.6 Corrective Actions and Preventative Actions (CAPA)

The CAPA operating plan is the essential instruction by which personnel plan to achieve correction of violative, unacceptable, and improper practices, and to prevent recurrence. CAPAs may arise from many sources, including deviations, customer complaints, investigations, internal audit findings, and external audit findings.

The quality unit must establish, monitor, and maintain a CAPA program. The CAPA program should include a tracking system for deviations, nonconformities, including out-of-specification laboratory results, and CAPAs. All persons must identify deviations and nonconformities and notify management and/or the quality unit. Supervisors must determine root causes and develop and implement appropriate remedial action(s), corrective action(s), and/or preventive action(s). The quality unit must monitor CAPAs and manage the CAPA program to assist with adequate development, implementation, and closure of CAPAs.

1.7 Supplier Qualification

A written risk-based supplier qualification program, where appropriate, must be established and implemented for components for which the manufacturer has identified a hazard that requires a supply-chain-applied control.

When a supply-chain applied control is applied by an entity other than the manufacturer's supplier (e.g., a component manufacturer applies controls that are under different management than the distributor supplying the component to the manufacturer), the manufacturer must verify the supply-chain control, or obtain documentation of appropriate verification activity from another entity, review and assess the entity's applicable documentation, and document that review and assessment. For the purposes of this section, verification means the application of methods, procedures, tests, and other evaluations, in addition to monitoring, to determine whether a control measure or combination of control measures is or has been operating as intended and to establish the validity of the safety plan [as specified in 21 CFR §117.126(b)].

The supplier qualification program must include:

- Using approved suppliers, and documenting that approval before receiving components from those suppliers;
- Determining appropriate supplier verification activities, including determining the frequency of conducting the activity by considering 21 CFR §§117.410(a)(2), 117.410(d), and 117.425:
    - The hazard analysis of the component, including the nature of the hazard controlled before receipt of the component;
    - The entity or entities that will be applying controls for the hazards requiring a supply-chain-applied control;
    - Supplier performance, including:
        - The supplier's procedures, processes, and practices inherent to the hazards associated with the component;
        - Applicable food safety regulations and information relevant to the supplier's compliance with those regulations, including warning letters or import alert relating to the safety of the component and other regulatory compliance actions related to component safety (or, when applicable, relevant laws and regulations and information relevant to the supplier's compliance with those laws and regulations);
        - The supplier's food safety history relevant to the component that the manufacturer receives from the supplier, including available information about results from testing components for hazards, audit results relating to the safety of the component, and responsiveness of the supplier in correcting problems; and
        - Any other factors as appropriate and necessary, such as storage and transportation practices;

- Conducting one or more supplier qualification activities for components and approving each supplier before using the component:
    - Risked-based supplier qualification activities may include:
        - On-site audits;
        - Sampling and testing of components (certificate of analysis verification);
        - Review of supplier's relevant food safety records; and
        - Other appropriate supplier verification activities based on supplier performance and the risk associated with the component;

- Documenting supplier qualification activities.

The manufacturer's supplier qualification management may require internal cross-functional support from procurement, research and development, manufacturing operations, quality unit operations, and regulatory affairs. Due to limited internal resources, if a large number of components are used by the manufacturer, risk management principles need to be applied to qualify suppliers of components. Quality risk factors to consider include the complexity of the supply chain, component characteristics, and the level of the supplier's technical performance and regulatory compliance. The risk-based supplier qualification program must be written, implemented, and followed.

Supplier qualification activities must be documented. Formal reports should be generated for each component from each supplier summarizing initial qualification activities and analyses, and plans and schedule for continuous monitoring. An approved list of components and suppliers should be readily available to staff. A unique component item code should be assigned for each component from each supplier; however, the manufacturer may identify equivalencies between the same components from different suppliers as long as they meet the same critical specification for identity, strength, purity, composition, and limits on contaminants.

Quality unit personnel must review and approve the documentation setting forth the basis for the qualification of any supplier.

1.8 Contract Manufacturers and Contract Laboratories

All contract manufacturers and contract laboratories should comply with the requirements of this general chapter or equivalent regulatory oversight system requirements. Special consideration should be given to the prevention of cross-contamination and to maintaining traceability.

Contract manufacturers and contract laboratories should be evaluated by the contract giver to ensure GMP compliance of the specific operations occurring at the contract sites.

There should be a written and approved contract or quality agreement between the contract giver and the contract acceptor that defines in detail the cGMP responsibilities, including the quality measures, of each party. The contract should include provisions for the contract giver to audit, onsite and/or virtual, the contract acceptor's facilities for compliance with GMPs. Where subcontracting is allowed, the contract acceptor should not pass to a third party any of the work entrusted to it under the contract without the contract giver's prior evaluation and approval of the arrangements.

Manufacturing and laboratory records should be kept at the site where the activity occurs and be readily available. Changes in the process, equipment, test methods, specifications, or other contractual requirements should not be made unless the contract giver has been informed and has approved the changes.

1.9 Complaints, Serious Adverse Event Reporting, and Recalls

1.9.1 COMPLAINTS

All quality related complaints, whether received orally or in writing, should be recorded and investigated according to written procedures.

Complaint records should include:

- Name and address of complainant;
- Name and phone number of person submitting the complaint;
- Name of dietary supplement, item code, and lot number;
- Nature of the complaint, including, if known, how the product was used;
- Date the complaint was received;
- Investigation undertaken and initial findings, including dates and identity of person(s) conducting the investigation;
- Action initially taken, including dates and identity of person(s) taking the action;
- Any follow up action taken;
- Response provided to the originator of the complaint, including date response was sent;
- Final findings and decision on product lot; and
- Quality unit personnel review and approval signature.

A qualified person must review and investigate all product complaints to determine whether the product complaint involves a possible failure of a dietary supplement to meet any of its specifications, or any other requirements of this general chapter, including those specifications and other requirements that, if not met, may result in risk of illness or injury.

Quality unit personnel must review and approve decisions about whether to investigate a product complaint and review and approve the findings and follow-up action of any investigation performed.

The review of the product complaint and any investigation performed must extend to all relevant batches and records.

Records of complaints should be retained in order to evaluate trends, product related frequencies, and severity with a view of taking additional, and if appropriate, immediate corrective action.

1.9.2 ADVERSE EVENT REPORTING

The manufacturer, packer, or distributor whose name appears on the label of a dietary supplement must maintain records related to dietary supplement adverse event reports that they receive, whether or not the adverse event is serious. The product labeling must include a continuously operating toll free telephone number for reporting adverse events involving the product. [NOTE—Products distributed with labels that do not contain the required telephone number or address are misbranded in the United States.]

All serious adverse event reports associated with the use of a dietary supplement must be submitted to the relevant regulatory agency, with a copy of the dietary supplement label, within 15 business days or within the time required by the regulatory authority after the report is received. [NOTE—In the United States, use MedWatch form FDA 3500A.]

If a retailer's name appears on the label as a distributor, the retailer may, by agreement, authorize the manufacturer or packer of the product to submit the required reports, as long as the retailer directs to the manufacturer or packer all adverse events associated with the product's use that are reported to it through the address or telephone number.

1.9.3 RETENTION OF ADVERSE EVENT REPORTING RECORDS

A responsible party must maintain records of any adverse event report it receives, whether serious or not, for 6 years from the date the report is received by the responsible party. Responsible parties must also give the authorized government officials timely access to the records. Responsible parties must maintain records containing the submission of serious-adverse-event reports, records containing submission of new medical information related to serious-adverse event reports, and records containing communications by the responsible party with anyone reporting a serious adverse event to the company. Responsible parties must maintain the records regardless of the source and regardless of any determination that the adverse event was caused by, or associated with, the product.

1.9.4 RECALLS

There should be a written procedure that defines the circumstances under which recall of a dietary supplement should be considered. The recall procedure should designate who should be involved in evaluating the information, how a recall should be initiated, who should be informed about the recall, and how the recalled dietary supplement should be treated. In the event of a serious or potentially life-threatening situation, local, national, and/or international regulatory authorities should be informed and regulations followed to ensure proper execution and disposition of the recall under international regulations.

Mock recalls should be performed annually.

1.10 Internal (Self-Inspection) Audits

In order to verify compliance with the requirements of this general chapter, regular internal audits should be performed according to an approved schedule. Audit findings and corrective actions should be documented and brought to the attention of responsible management. Acceptable corrective action should be completed in a timely and effective manner.

1.11 Product Quality Review

Regular quality reviews of dietary supplements should be conducted annually with the objective of verifying the consistency of the manufacturing process.

Such review should normally be conducted annually and should include a review of:

- Critical dietary supplement test results;
- All batches that failed to meet established specification(s);
- Critical deviations or nonconformities and related investigations;
- Adequacy of corrective actions;
- Changes to the manufacturing process and analytical procedures;
- Results of the stability monitoring program; and
- Quality-related returns, complaints, and recalls.

The results of this review should be evaluated and an assessment made of whether any additional corrective action or any revalidation should be undertaken. Reasons for such corrective actions should be documented. Acceptable corrective actions should be completed in a timely and effective manner.

1.12 Quality Management Documentation

The following documentation must be made and kept for fulfilling the requirements of the Quality Management System (quality system 1).

1.12.1 WRITTEN PROCEDURES

Written procedures must be established and followed for:

- Creating and maintaining job position descriptions, listing job responsibilities and required qualifications for education, training and experience;
- Implementing a training program;
- Implementing a documentation and records control management system;
- Implementing a change control program;
- Implementing a deviation management program;
- Conducting material reviews;
- Implementing a corrective action and preventive action management program;
- Implementing a supplier qualification program;
- Implementing contract (manufacturing and laboratory) services program;
- Implementing a complaints handling program;
- Handling recalls;
- Conducting internal audits; and
- Conducting product quality reviews.

1.12.2 RECORDS

Records must be made and kept for:

- Organizational chart and job position descriptions; curriculum vitae should be available for all key management individuals in operations and quality;
- Training, including the date of the training, the type of training, name of trainer if applicable, the person(s) trained, and any assessment results (e.g., test results);
- List of and copies of current standard operating procedures, master manufacturing records, and standard test methods;
- List of and reports of changes that affect the production and quality of dietary supplements;
- List of and reports of unanticipated occurrences and deviations from approved instructions or established standards;
- List of and copies of executed batch manufacturing records;
- List of and reports of material reviews;
- List of and reports of corrective actions and preventative actions taken;

- List of approved suppliers of components, packaging materials, and labeling, and corresponding supplier qualification evaluation reports;
- List of approved suppliers of manufacturing and laboratory services, and corresponding evaluation reports, and quality agreements;
- List of complaints and corresponding investigation reports;
- Recall and mock recall reports;
- Internal (self-inspection) audit schedule and reports; and
- Product quality review reports.

2. PHYSICAL PLANT AND EQUIPMENT

2.1 Grounds Maintenance

The grounds around the physical plant must be kept in a condition that protects against the contamination of components, in-process material, dietary supplements, and contact surfaces. The methods for adequate ground maintenance include the following:

- Properly storing equipment, removing litter and waste, and cutting weeds or grass within the immediate vicinity of the physical plant so that it does not constitute an attractant, breeding place, or harborage for pests;
- Maintaining roads, yards, and parking lots so that they do not constitute a source of contamination in areas where components, in-process material, dietary supplements, or contact surfaces are exposed;
- Adequately draining areas that may contribute to the contamination of components, in-process materials, dietary supplements, or contact surfaces by seepage, filth, or any other extraneous materials, or by providing a breeding place for pests;
- Adequately operating systems for waste treatment and disposal so that they do not constitute a source of contamination in areas where components, in-process materials, dietary supplements, or contact surfaces are exposed;
- If the physical plant grounds are bordered by grounds not under the operator's control and not maintained in the aforementioned manner, care must be exercised in the plant by inspection, extermination, or other means to exclude pests, dirt, filth, or any other extraneous materials that may be a source of contamination.

2.2 Physical Plant Design

Any physical plant used in the manufacture of dietary supplements must be of suitable size, construction and design to facilitate maintenance, cleaning, and sanitizing operations. The physical plant must have adequate space for the orderly placement of equipment and holding of materials as is necessary for maintenance, cleaning, and sanitizing operations, and to prevent contamination and mix-up of materials. The flow of materials and personnel throughout the physical plant should be designed to prevent contamination and mix-up of materials.

2.2.1 SEPARATE AND DEFINED AREAS

The physical plant must have and the manufacturer must use separate, defined areas of adequate size or other control systems—such as computerized inventory controls or automated systems of separation, physical or spatial separation—to prevent contamination or allergen cross-contact and mix-up of components, in-process materials, dietary supplements, packaging materials, and labels, during the following operations:

- Receiving, identifying, sampling, holding, and withholding from use materials to be used in manufacturing;
- Separating materials to be used in manufacturing from materials awaiting material review and disposition (i.e., in quarantine);
- Performing production, packaging, labeling, and holding operations;
- Physically separating allergen-containing raw materials from non-allergen raw materials;
- Holding rejected materials before further disposition (e.g., return, reprocessing, or destruction);
- Performing and separating the manufacturing, packaging, labeling, and holding of different product types, including different types of dietary supplements, and other foods, cosmetics, and pharmaceutical products;
- Cleaning and sanitizing contact surfaces;
- Performing and separating chemical and microbiological laboratory analyses and holding of laboratory samples and supplies.

Laboratory areas/operations should normally be separated from production areas. Some laboratory areas, particularly those used for in-process controls, can be located in production areas, provided the operations of the production process do not adversely affect the accuracy of the laboratory measurements, and the laboratory and its operations do not adversely affect the production process.

Dedicated production areas, which can include facilities, air handling equipment and/or process equipment, should be considered when materials of an allergenic nature are involved, unless validated cleaning procedures are established and maintained.

2.2.2 DESIGN AND CONSTRUCTION

The physical plant must be designed and constructed in a manner that prevents contamination of materials and contact surfaces by having the following:

- Floors, walls, and ceilings that can be adequately cleaned and kept in good repair;
- Fixtures, ducts, and pipes that do not contaminate materials and contact surfaces by dripping or other leakage, or condensate;
- Adequate ventilation or environmental control equipment such as airflow systems, including filters, fans, and other air-blowing equipment that minimize odors and vapors (including steam and noxious fumes) in areas where they may cause allergen cross-

contact or contamination of materials or contact surfaces, and that are located and operated in a manner that minimizes the potential for allergens, microorganisms, and particulate matter to contaminate materials or contact surfaces;

- Equipment that controls air pressure, temperature, and humidity, as needed to ensure the quality of the dietary supplement; particular attention should be given to areas where components, in-process materials, and dietary supplements are exposed to the environment;
- Aisles or working spaces between equipment and walls that are adequately unobstructed and of adequate width to permit staff to perform their duties and to protect against contamination of materials and contact surfaces with clothing or personal contact;
- Adequate lighting in all areas where material is examined, processed, or held, or where contact surfaces are cleaned; and in hand-washing areas, dressing and locker rooms, and bathrooms;
- Safety-type light bulbs, fixtures, skylights, or other glass or glass-like materials when suspended over exposed materials in any step of manufacture;
- Adequate screening or other protection against pests and insects, where necessary;
- Adequate protection of materials in bulk fermentation vessels by, for example, use of protective coverings; placement in areas where harborages for pests can be eliminated over and around the vessels; placement where staff can check regularly for pests, pest infestation, filth, biofilm, organic material, or any other extraneous materials; or by use of skimming equipment.

2.3 Physical Plant Sanitation and Facilities

The physical plant must be kept clean and sanitary, and maintained in repair sufficient enough to prevent materials and contact surfaces from becoming contaminated.

Written procedures should be established assigning responsibility for sanitation and describing the cleaning schedules, methods, equipment, and materials to be used in cleaning buildings and facilities.

Utilities that could affect dietary supplement quality (e.g., purified water, potable water, steam, gases, compressed air, heating, ventilation, and air conditioning) should be qualified and appropriately monitored and action should be taken when acceptance criteria are not met. Drawings for these utility systems should be made and available.

2.3.1 Cleaning Compounds, Sanitizing Agents, Pesticides, and Other Toxic Materials

Cleaning compounds and sanitizing agents must be free from undesirable microorganisms and must be safe and adequate under the conditions of use. All toxic materials should be purchased with a safety data sheet and supplier's guarantee or certification. Toxic materials must not be used or held in the physical plant in which components, in-process materials, dietary supplements, and contact surfaces are manufactured or exposed, unless those materials are required to maintain clean and sanitary conditions, to conduct laboratory test procedures, to maintain or operate the physical plant or equipment, or to use in the physical plant's operations. Toxic materials must be identified and held in a manner that protects against contamination of components, in-process materials, dietary supplements, and contact surfaces. All relevant federal, state, and local government regulations for the use and holding of these toxic materials must be followed.

Any substances associated with the operation of equipment, such as lubricants, heating fluids, or coolants, should not contact in-process materials or dietary supplements so as to alter their quality beyond established specifications. Any deviations from this should be evaluated to ensure that there are no detrimental effects upon the suitability for use of the material. When possible, food grade lubricants and oils should be used. When the lubricant used is placed in direct contact with an in-process material (e.g., in the production of soft gelatin capsule film) a food grade is required.

2.3.2 Pest Control

Animals or pests must not be allowed in any area of the physical plant. Effective measures must be taken to exclude pests from the physical plant and to protect against contamination of materials and contact surfaces on the premises by pests. The use of pesticides, such as insecticides, fumigants, fungicides, or rodenticides, is permitted only if precautions are taken to protect against the contamination of components, in-process materials, dietary supplements, and contact surfaces. Pesticides should be registered and used in accordance with the Federal Insecticide, Fungicide, and Rodenticide Act.

2.3.3 Water Supply

Potable water at a suitable temperature, and under pressure as needed, must be supplied in a plumbing system free of defects that protects against contamination or undesirable chemical reaction of components, in-process materials, dietary supplements, and contact surfaces. Potable water must meet, at minimum, all the requirements for drinking water promulgated in the U.S. Environmental Protection Agency's National Primary Drinking Water Regulations (40 CFR §141), and any applicable state and local drinking water requirements that are more stringent. For manufacturers outside the U.S., potable water meeting equivalent requirements may be acceptable with justification, for example, the drinking water regulations of the European Union (European Commission Directive 98/93/EC) or Japan Drinking Water Quality Standards. Water not meeting such requirements should not be permitted for use in the water purification system for *Purified Water*.

If water is to be used as a component of a dietary supplement, e.g., when such water contacts components, in-process materials, dietary supplements, or any contact surface, it should be assessed to ensure that the quality of such water does not negatively affect the quality of the dietary supplement over its designated shelf life. Where water used in the manufacturing process is treated by the manufacturer to achieve a defined quality, the treatment process should be qualified and monitored with appropriate acceptance and action level criteria.

Water from a private source should be used in a manner such that the water may become a component of the dietary supplement, comply with any state and local requirements, and not contaminate the dietary supplement. Satisfying this requirement may involve performing appropriate water treatment procedures, including filtration, sedimentation, and chlorination.

2.3.4 PLUMBING

The plumbing in the physical plant must be of an adequate size and design and be adequately installed and maintained to:

- Carry sufficient amounts of water to the required locations throughout the physical plant;
- Properly convey sewage and liquid disposable waste from the physical plant;
- Avoid being a source of contamination to components, in-process materials, dietary supplements, or any contact surface, or creating an unsanitary condition;
- Provide adequate floor drainage in all areas where floors are subject to flooding-type cleaning or where normal operations release or discharge water or other liquid waste on the floor; and
- Not allow backflow from, or cross connection between piping systems that discharge waste water or sewage and piping systems that carry water used for manufacturing dietary supplements, for cleaning contact surfaces, or for use in bathrooms or hand-washing facilities.

Permanently installed pipework should be appropriately identified. This can be accomplished by identifying individual lines with content and directional flow arrows, documentation of computer control systems, or alternative means.

2.3.5 SEWAGE AND TRASH DISPOSAL

Sewage, refuse, and other waste in and from buildings and the immediate surrounding area should be disposed of in a safe, timely, and sanitary manner. Sewage must be disposed of into an adequate sewage system. Trash and hazardous waste must be conveyed, stored, and disposed of in a manner to minimize the development of odors; minimize the potential for the trash to attract, harbor, or become a breeding place for pests; and protect against contamination of materials, contact surfaces, water supplies, and grounds surrounding the physical plant. Containers and/or pipes for waste material should be clearly identified.

2.3.6 BATHROOMS AND HAND-WASHING FACILITIES

Adequate and readily accessible bathrooms and hand-washing facilities must be provided and kept clean, and must not be a potential source of contamination of materials and contact surfaces. The facilities must be designed to provide water at a suitable temperature, soap and sanitizing agents, air driers, or single-service towels [cGMP, 21 CFR §111.15(h)–(i)]. Adequate facilities for showering and/or changing clothes should be provided, when appropriate.

2.3.7 ALLERGEN CROSS-CONTAMINATION REDUCTION CONTROL

Adequate precautions must be taken to reduce the potential for allergen cross-contact of components, in-process materials, dietary supplements, and contact surfaces by adequate food safety controls and operating practices or effective design of the physical plant, including the separation of operations in which allergen cross-contact is likely to occur, by one or more of the following means: location, time, partition, air flow systems, dust control systems, enclosed systems, or other effective means [cGMP, 21 CFR §117.20(b)(2)].

2.3.8 SANITATION SUPERVISORS

One or more employees must be assigned to supervise overall sanitation, and must be qualified by education, training, and/or experience to develop and supervise sanitation procedures, using appropriate risk-based assessments and preventative controls.

2.4 Equipment, Instruments, and Utensils

Equipment, instruments, and utensils used in the manufacture of dietary supplements must be of appropriate design, construction, and workmanship, to enable them to be suitable for their intended use and suitably located to facilitate operations for their intended use and to be adequately cleaned and properly maintained.

Equipment and utensils include, but are not limited to, the following: equipment used to hold or convey; equipment used to measure (i.e., instruments); equipment using compressed air or gas; equipment used to carry out processes in closed pipes and vessels; and equipment used in automatic, mechanical, or electronic systems.

Major equipment and permanently installed processing lines used during the production, packaging, and labeling of dietary supplements should be appropriately identified. A set of current drawings and/or manuals should be maintained for equipment and critical installations (e.g., instrumentation and utility systems). Equipment should be identified as to its contents and its cleanliness status by appropriate means.

2.4.1 DESIGN AND CONSTRUCTION

Equipment and utensils must be appropriate in design and construction to:

- Prevent contamination of components, packaging materials, in-process materials, or finished product with lubricants, fuel, coolants, metal or glass fragments, filth or any other extraneous material, contaminated water, or any other contaminants;
- Be corrosion-resistant and made of nontoxic materials if the equipment or utensils contact components, in-process materials, or dietary supplements;
- Withstand the environment in which they are used in manufacturing, cleaning, and sanitizing;
- Must have seams that are smoothly bonded or maintained to minimize accumulation of dirt, filth, biofilm, organic material, particles of components, in-process materials, dietary supplements, or any other extraneous materials or contaminants;
- Constructed so that surfaces that contact components, in-process materials, or dietary supplements are not corrosive, reactive, additive, or absorptive so as to alter the quality of the product beyond the established requirements.

Automated, mechanical, or electronic equipment that is used to manufacture, package, label, or hold a dietary supplement must be designed or selected to ensure that the dietary supplement specifications are consistently met.

The suitability of the equipment must be determined by ensuring that the equipment is capable of operating satisfactorily within the operating limits required by the process.

2.4.2 INSTALLATION AND MAINTENANCE

Equipment and utensils must be installed and maintained to facilitate cleaning the equipment and utensils and adjacent spaces, and to protect components, in-process materials, and dietary supplements from being contaminated by any source.

Each freezer, refrigerator, and cold storage compartment used to hold components, in-process materials, or dietary supplements:

- Must be fitted with a calibrated indicating thermometer, temperature-measuring device, or temperature-recording device that shows, indicates, and records, or allows for recording by hand, the temperature accurately within the compartment. If recording by hand, monitoring must occur at a frequency established according to risk management principles.
- Must have an automated device for regulating temperature or an automated alarm system to indicate a significant temperature change in a manual operation.

Compressed air or other gases introduced mechanically into or onto components, in-process materials, dietary supplements, or contact surfaces, or that are used to clean any contact surface, must be treated in such a way (e.g., proper filtration) that the component, in-process material, dietary supplement, or contact surface is not contaminated.

Instruments or controls used in the manufacturing, packaging, labeling, or holding of a dietary supplement, and instrument controls used to measure, regulate, or record temperatures, pH, water activity, or other conditions, and to control or prevent the growth of microorganisms or other contamination must be accurate and precise, calibrated periodically, adequately maintained, and adequate in number for their designated uses.

2.4.3 OPERATION AND CALIBRATION

Control, weighing, measuring, monitoring, and test equipment, i.e., instruments and controls, which are critical for assuring the quality of dietary supplements, must be calibrated according to written procedures and an established schedule. Equipment and instruments used in the manufacture of dietary supplements must only be used within its qualified operating range. Equipment calibrations should be performed using compendial reference standards, or standards traceable to certified standards, if available.

Instruments and controls used in manufacturing or testing a component, in-process material, or dietary supplement must be calibrated against a reference standard before first use; at a frequency specified in writing by the manufacturer of the instrument or control, and at routine intervals or as otherwise necessary to ensure the accuracy and precision of the instrument and control.

Instruments or controls that cannot be adjusted to agree with the reference standard must be repaired or replaced.

Balances used to accurately weigh material should comply with *Balances* ⟨41⟩ and *Weighing on an Analytical Balance* ⟨1251⟩. This should include the determination and posting of the minimum accurate weight on all scales and balances used throughout the production and laboratory testing units.

Automated, mechanical, or electronic equipment that is used to manufacture, package, label, or hold a dietary supplement must be routinely calibrated, inspected, or checked to ensure proper performance. The quality unit must periodically approve these calibrations, inspections, or checks.

The appropriate controls for automated, mechanical, and electronic equipment (including software for a computer-controlled process) must be established and used to ensure that any changes to the manufacturing, packaging, labeling, holding, or other operations are approved by the quality unit and instituted only by authorized personnel.

The appropriate controls must be established and used to ensure that the equipment functions in accordance with its intended use. These controls must be approved by the quality control unit.

Deviations from approved standards of calibration on critical instruments should be investigated to determine if these could have had an impact on the quality of in-process materials or dietary supplements using this equipment since the last successful calibration.

Quality unit personnel must:

- Review and approve all processes for calibrating equipment and instruments;
- Periodically review all records for calibration of equipment, instruments, and controls;
- Periodically review all records for calibrations, inspections, and checks of automated, mechanical, or electronic equipment; and
- Review and approve controls to ensure that automated, mechanical, or electronic equipment functions in accordance with its intended use.

2.4.4 CLEANING AND MAINTENANCE

Equipment, utensils, and any other contact surfaces used to manufacture, package, label, or hold components, in-process materials, or dietary supplements must be maintained, cleaned, and sanitized, as necessary, to protect against allergen cross-contact and contamination of components, in-process materials, and dietary supplements. Equipment and utensils must be taken apart as necessary for thorough maintenance, cleaning, and sanitizing.

Schedules and procedures, including assignment of responsibility, should be established for the preventative maintenance of equipment.

Written procedures should be established for cleaning of equipment and its subsequent release for use in the manufacture of dietary supplements. Cleaning procedures should contain sufficient details to enable operators to clean each type of equipment in a reproducible and effective manner. These procedures should include:

- Assignment of responsibility for cleaning of equipment;
- Cleaning schedules, and sanitizing schedules as needed;
- Complete description of the methods and materials, including dilution of cleaning agents used to clean equipment;
- Instructions, as needed, for disassembling and reassembling each part of equipment to ensure proper cleaning;
- Instructions for the removal or obliteration of previous batch identification;
- Instructions for the protection of clean equipment from contamination prior to use, and the maximum time that may elapse between completion of cleaning and use in manufacturing;
- Inspection of equipment cleanliness immediately before use; and
- Establishing the maximum time that may elapse between the completion of manufacturing processing and equipment cleaning.

All contact surfaces must be cleaned and sanitized, as necessary, before use and after any interruption during which the contact surfaces may have become contaminated. In consecutive operations involving batches of different dietary supplements, the contact surfaces must be adequately cleaned, and sanitized as needed, to prevent cross-contamination; in consecutive operations involving different batches of the same dietary supplement, the contact surfaces must be inspected, and adequately cleaned and sanitized, as necessary to prevent buildup and carry-over of contaminants (e.g., objectionable levels of microorganism). Acceptance criteria for residues and the choice of cleaning procedures and cleaning agents should be defined and justified. The cleaning status of equipment should be stated on the equipment.

Surfaces that do not come into direct contact with components, in-process materials, or dietary supplements must be cleaned as frequently as necessary to protect against contaminating components, in-process materials, or dietary supplements.

Effective systems should be used to reduce the potential of non-contact surfaces from becoming sources of contamination, such as floor sticky pads between different production areas and a captive shoe policy and program.

Plastic pallets should be used in high risk areas where components, in-process materials, dietary supplements, and contact surfaces are exposed. At minimum, heat treated pallets must be used in areas where components, in-process materials, dietary supplements, and contact surfaces are exposed. An effective pallet cleaning, maintenance, inspection, and management program must be established, documented, and followed.

Contact surfaces used for manufacturing or holding low-moisture components, in-process materials, or dietary supplements must be in a clean, dry, sanitary condition before use. When the surfaces are wet-cleaned, they must be sanitized, when necessary, and thoroughly dried before subsequent use.

If wet processing is used during manufacturing, all contact surfaces must be cleaned and sanitized, as necessary, to protect against the introduction of microorganisms into components, in-process materials, or dietary supplements. When cleaning and sanitizing is necessary, all contact surfaces must be cleaned and sanitized before use and after any interruption during which the contact surface may have become contaminated. In a continuous production operation or in consecutive operations involving different batches of the same dietary supplement, the contact surfaces must be adequately cleaned and sanitized, as necessary.

Single-service articles (such as utensils intended for one-time use, paper cups, and paper towels) must be stored in appropriate containers; and handled, dispensed, used, and disposed of in a manner that protects against contamination of components, in-process materials, dietary supplements, or any contact surface.

Cleaning compounds and sanitizing agents must be adequate for their intended use and safe under their conditions of use.

The portable equipment and utensils that have contact surfaces must be cleaned, sanitized, and stored in a location and manner that protects them from contamination.

2.4.5 EQUIPMENT AND INSTRUMENT QUALIFICATION

Equipment and instruments must be demonstrated to be “fit for purpose.” There are many ways of demonstrating that equipment and instruments are “fit for purpose” and under control, and these can include qualification, calibration, and maintenance. Equipment or instrument qualification activities necessary to establish “fitness for purpose” may be grouped into four phases: design qualification (DQ), installation qualification (IQ), operational qualification (OQ), and performance qualification (PQ). In order to ensure “fitness for purpose”, an integrated approach, based upon a risk assessment, should be undertaken.

A variety of equipment and instruments, ranging from a simple apparatus to complex computerized systems, is used in the dietary supplement industry to manufacture, package, label, test, and hold dietary supplements. The risk assessment enables the classification of equipment and instruments to determine the extent of qualification and actions needed to demonstrate “fitness for purpose.” Generally, the more complex the equipment or instrument, or the higher the criticality of its operation, the greater the amount of work required to ensure “fitness for purpose.”

Requirements for the intended use should be appropriately defined to ensure that the particular needs and technical and operational requirements are met. Qualification activities are described in *Analytical Instrument Qualification* ⟨1058⟩.

When an equipment or instrument undergoes major repairs or modifications, this should be evaluated using change control. Relevant equipment qualification should be repeated to verify that the equipment continues to operate satisfactorily. If equipment is moved to another location, an assessment should be made of what, if any, qualification stage should be repeated.

2.4.6 Computerized systems

Written procedures should be available for the operation and maintenance of computerized systems.

Appropriate installation qualification and operational qualification should demonstrate the suitability of the computer hardware and software to perform assigned tasks.

GMP related computerized systems must be validated. The depth and scope of validation depends on the diversity, complexity, and criticality of the computerized application. Commercially available software that has been validated may require an abbreviated level of testing. If an existing system was not validated at time of installation, a retrospective validation could be conducted if appropriate documentation is available.

Where critical data are being entered manually, there must be an additional check on the accuracy of the entry. This can be done by a second operator or by the system itself, e.g., barcode reader.

Changes to the computerized system must be made according to a change control procedure and should be formally authorized, documented, and tested. Records must be kept of all change, including modifications and enhancements made to hardware and software. These records should demonstrate that the system is maintained in a validated state.

If system breakdowns or failures would result in the permanent loss of records, a back-up system should be provided. A means of ensuring data protection should be established for all GMP related computerized systems. Data can be recorded by a second means in addition to the computer system.

All electronic records must comply with 21 CFR Part 11—*Electronic Records; Electronic Signatures*.

2.4.6.1 Computer systems procedures and controls: GMP related computerized systems used to create, modify, maintain, or transmit electronic records must employ procedures and controls designed to ensure the authenticity, integrity, and, when appropriate, the confidentiality of electronic records, and to ensure that the signer cannot readily repudiate the signed record as not genuine. Such procedures and controls must include, but are not limited to, the following:

- Validation of systems to ensure accuracy, reliability, consistent intended performance, and the ability to discern invalid or altered records;
- The ability to generate accurate and complete copies of records (including controls to prevent omissions in data, e.g., system turned off and data not captured) for inspection, review, and copying;
- Protection of records to enable their accurate and ready retrieval throughout the records retention period;
- Limiting system access to authorized individuals to prevent unauthorized access or changes to data;
- Use of secure, computer-generated, time-stamped audit trails to independently record the date and time of operator entries and actions that create, modify, or delete electronic records;
- Establishment of, and adherence to, written policies that hold individuals accountable and responsible for actions initiated under their electronic signatures in order to deter record and signature falsification;
- Use of appropriate controls over systems documentation including distribution of, access to, and use of documentation for system operation and maintenance; and revision and change control procedures to maintain an audit trail that documents time-sequenced development and modification of systems documentation.

2.4.6.2 Electronic signatures: Signed electronic records must contain information associated with the signing that clearly indicates all of the following: the printed name of the signer, the date and time when the signature was executed, and the task performed (such as review, approval, responsibility, or authorship) associated with the signature.

Each electronic signature must be unique to one individual and must not be reused by, or reassigned to, anyone else. Electronic must employ at least two distinct identification components such as an identification code and password. Persons who used electronic signatures must employ controls to ensure their security and integrity.

2.5 Physical Plant and Equipment Documentation

The following documentation must be made and kept for fulfilling the requirements of the Physical Plant and Equipment System (quality system 2).

2.5.1 Written procedures

Written procedures must be established and followed for:

- Maintaining, cleaning, and sanitizing, as necessary, the physical plant and facilities;
- Pest control;
- Maintaining, cleaning, and sanitizing, as necessary, equipment, utensils, and any other contact surfaces that are used to manufacture, package, label, or hold components in-process materials, and dietary supplements;
- Use of cleaning compounds, sanitizing agents, pesticides, and other toxic materials;
- Pallet inspection;
- Equipment and instrument qualification;
- Calibrating instruments and controls used in manufacturing or testing a component, in-process material, or dietary supplement;
- Calibrating, inspecting, and checking automated, mechanical, and electronic equipment and instruments; and
- Operating and maintaining GMP related computerized systems.

2.5.2 Records

Records must be made and kept for:

- List of approved cleaning compounds, sanitizing agents, and corresponding safety data sheets;
- Drawings for utility systems, e.g., water, steam, gases, compressed air, heating, ventilation, and air conditioning;
- Physical plant and facility maintenance, cleaning and sanitizing schedules, and logs of the date of maintenance, cleaning, and sanitizing, as necessary, unless such documentation is kept with the batch record;

- Pest control;
- Demonstrating that water, when used in as a component of a dietary supplement, meets the relevant Compendial requirements;
- List of manufacturing equipment and instrumentation;
- Drawings and/or manuals for equipment and critical installations;
- Documentation, in individual equipment logs, of the date of use, maintenance, cleaning, and sanitizing of equipment, unless such documentation is kept with the batch record;
- Documentation of the controls used to ensure that equipment and instruments function in accordance with their intended use;
- Documentation of any calibration, each time the calibration is performed, for instruments and controls used in manufacturing or testing a component, in-process materials, or dietary supplement:
    - The documentation must identify the instrument or control calibrated and date of calibration, identify the reference standard used including the certification of accuracy of the reference standard and history of recertification of accuracy, identify the calibration method used including appropriate acceptance limits for accuracy and precision of instruments and controls when calibrating, provide the calibration reading(s) found, identify the recalibration method used and reading(s) found if accuracy and/or precision acceptance limits were not met, and initials of the person who performed the calibration or recalibration;

- Documentation of pallet inspection and disposition;
- Documentation of equipment and instrument qualification;
- Documentation of calibrations, inspections, and checks of automated, mechanical, and electronic equipment; and
- Backup file(s) of current and outdated software, as necessary, to retrieve records that are required to be kept, and of data entered into the computer system used to manufacture, package, label, and hold dietary supplements:
    - Backup file(s) (e.g., a hard copy of data entered, tapes, compact disks, flash drives) must be an exact and complete record of the date entered, and must be kept secure from alterations, inadvertent erasures, or loss.

3. MATERIALS MANAGEMENT OPERATIONS AND CONTROLS

The persons authorized to release components, packaging materials, labeling, and dietary supplements should be specified. No materials should be released or used before the satisfactory completion of evaluation by the quality unit(s) unless there are appropriate systems in place to allow for such use (e.g., release under quarantine, see distribution procedures).

3.1 Establishing Material and In-Process Production Specifications

Specifications must be established for any point, step, or stage in the manufacturing process where control is necessary to ensure the quality of the dietary supplement and that the dietary supplement is packaged and labeled as specified in the master manufacturing and packaging control record.

3.1.1 COMPONENT SPECIFICATIONS

Specifications must be established for each component that is used in the manufacture of a dietary supplement to ensure that the specifications for the purity, strength, and composition of the dietary supplement, manufactured using the components, are met. The specification for the components should include specifications for:

- Identity;
- Purity;
- Content or assay;
- Limits on contaminants that may adulterate or may lead to adulteration of the finished batch of dietary supplements;
- Applicable specific tests (e.g., peroxide value, anisidine value for oil rancidity);
- Physical characteristics impacting manufacturing process (e.g., particle size, bulk density);
- Special claims should also be included in the specifications and be verified by the user of the material. Special claims include gluten-free, no soy, no dairy, etc.

Generally, dietary supplements are prepared from ingredients that meet *USP*, *NF*, or *Food Chemical Codex* standards. Where such standards do not exist, substances may be used in dietary supplements if they have been shown to be of acceptable food grade quality using other suitable procedures.

The purity of water used as a component of a dietary supplement should be appropriately defined to maintain the stability of the dietary supplement throughout its shelf life.

Ingredients may be added to dietary supplements provided that the ingredients comply with applicable regulatory requirements, and do not interfere with the assay and tests prescribed for determining compliance with the bulk or finished dietary supplement specification.

Adequate documentation must be provided for the basis for why the component specifications will help ensure that the specifications are met for the identity, purity, strength, and composition of the dietary supplements and for limits on those types of contamination that may adulterate or may lead to adulteration of the finished batch of the dietary supplement.

Each component received from a supplier that is liable to contamination with microorganisms, filth, insect infestation, allergens, aflatoxins, other natural toxins, pesticides, organic impurities, residual solvents, inorganic impurities, elemental contaminants, foreign substances, or other extraneous substances that may be a source of contamination that is objectionable in view of its intended use must be tested or examined against established specifications for such contamination. Applicable *USP* general chapters should be used, including the following:

Residual Solvents ⟨467⟩

Articles of Botanical Origin ⟨561⟩, *Test for Aflatoxins* and *Pesticide Residue Analysis*

Microbial Enumeration Tests ⟨2021⟩

Absence of Specified Microorganisms ⟨2022⟩

Microbiological Attributes of Nonsterile Nutritional and Dietary Supplements ⟨2023⟩

Elemental Contaminants in Dietary Supplements ⟨2232⟩

3.1.2 IN-PROCESS PRODUCTION SPECIFICATIONS

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

Adequate documentation must be provided for the basis for why meeting the in-process specifications, in combination with meeting component specifications, will help ensure that the specifications are met for the identity, purity, strength, and composition of the dietary supplements and for limits on those types of contamination that may adulterate or may lead to adulteration of the finished batch of the dietary supplement. Quality unit personnel must review and approve this documentation.

3.1.3 LABELING AND PACKAGING MATERIAL SPECIFICATIONS

Specifications must be established for labeling (label specifications, see *Labeling* ⟨7⟩) and packaging materials that come in contact with dietary supplements (packaging specifications, see *Packaging and Storage Requirements* ⟨659⟩, *Containers—Glass* ⟨660⟩, *Plastic Packaging Systems and Their Materials of Construction* ⟨661⟩, *Plastic Materials of Construction* ⟨661.1⟩, *Plastic Packaging Systems for Pharmaceutical Use* ⟨661.2⟩, *Auxiliary Packaging Components* ⟨670⟩, and *Containers—Performance Testing* ⟨671⟩). Packaging that may come into contact with dietary supplements must be safe and suitable for its intended use and must not be reactive or absorptive or otherwise affect the safety or quality of the dietary supplement.

3.1.4 IN-PROCESS (BULK) DIETARY SUPPLEMENT SPECIFICATIONS

Specifications must be established for each dietary supplement that is manufactured. The specification for the dietary supplement should include specifications for:

- Identity;
- Purity;
- Strength or composition (i.e., content or assay);
- Limits on contaminants that may adulterate or may lead to adulteration of the finished batch of dietary supplements;
- Applicable specific characteristics (e.g., peroxide value, anisidine value for oil rancidity);
- Performance (i.e., disintegration and/or dissolution);
- Dosage forms quality tests (e.g., tablet friability, weight variation, or content uniformity).

Dietary supplements for which a monograph is provided in the *USP* should comply with the monograph standard and other applicable standards in that compendium.

Defect action levels: Some dietary supplements, even when produced under good manufacturing practices, contain naturally occurring unavoidable defects that at low levels present no health hazard. Defect action levels are set because it is economically impractical to grow, harvest, or process raw products that are totally free of non-hazardous, naturally, unavoidable defects. Products harmful to consumers are subject to regulatory action whether or not they exceed the defect action levels. The manufacturer, packer, and holder of a dietary supplement must, at all times, utilize quality unit operations that reduce natural or unavoidable defects to the lowest level currently feasible. The mixing of a dietary supplement containing defects at levels that render that dietary supplement adulterated with another lot of dietary supplement is not permitted and renders the final dietary supplement adulterated, regardless of the defect action level of the final dietary supplement.

3.1.5 RECEIVED IN-PROCESS (BULK) DIETARY SUPPLEMENT SPECIFICATIONS

Specifications must be established for an in-process (bulk) dietary supplement received from a supplier for packaging and labeling, and for distribution. The specification must provide sufficient assurance that the in-process (bulk) dietary supplement received is adequately identified, consistent with the purchase order, and the CoA meets agreed-upon specifications or supplier quality agreement.

3.1.6 FINISHED DIETARY SUPPLEMENT SPECIFICATIONS

Specifications must be established for the packaging and labeling of the finished packaged and labeled dietary supplements that ensures that the correct packaging and labeling was used.

3.2 Determining Compliance with Specifications

[NOTE—*General Notices* should apply.]

3.2.1 GENERAL

Quality unit personnel must determine whether the specifications set for components, in-process materials, packaging materials, labeling, in-process (bulk) dietary supplements, received in-process (bulk) dietary supplements, and finished dietary supplements are met.

Quality control (laboratory control) unit personnel must conduct the necessary tests to determine whether the specifications for components, in-process materials, and dietary supplements comply with specifications. On the basis of adequate process verification, in-process controls, and statistical confidence, a reduced testing (or sampling) plan is an alternative to fully testing every batch of material, provided that:

- For components, at least one identification test or examination with sufficient specificity is conducted;
- For packaging material and labeling, at least one identification test is conducted;
- For dietary supplements, at least one measure representative of the overall quality is performed.

Tests that are used to determine whether material specifications are met must be appropriate for their intended use and must be validated methods according to *Validation of Compendial Procedures ⟨1225⟩*.

The quality control unit must conduct an out-of-specification investigation and corrective action plans must be established for use when an established specification is not met.

3.2.2 COMPONENTS

Before any component is used in manufacturing, at least one appropriate test or examination must be conducted to verify the identity of the component, and determine whether other applicable component specifications are established by doing the following:

- Conduct appropriate tests or examinations for all of the test specifications; or
- Rely on the certificate of analysis from the supplier of the component received, provided that:
    - The supplier is qualified by establishing the reliability of the supplier's certificate of analysis through confirmation of the results through independent tests, on-site audit, and other appropriate supplier qualification activities;
    - The certificate of analysis includes a description of the specific tests or examination methods used (i.e., specific reference to a test procedure that can be performed by an experienced scientist); acceptance criteria for the tests or examinations, and actual results of the tests or examinations;
    - Documentation is maintained of how the supplier was qualified;
    - The reliability of the supplier's certificate of analysis is periodically re-confirmed by conducting independent tests for the specifications that consistently confirm the values shown in the certificate of analysis;
    - Quality unit personnel have reviewed and approved the documentation setting forth the basis for qualification and re-qualification of the supplier.

3.2.3 IN-PROCESS PRODUCTION

In-process points, steps, or stages where control is necessary to ensure the quality of the finished batch of dietary supplements must be monitored to determine whether in-process specifications are met; and to detect any deviation or unanticipated occurrence that may result in the failure of the dietary supplement to meet specifications.

3.2.4 DIETARY SUPPLEMENTS

For a subset of dietary supplement batches (for in-process (bulk) dietary supplements and/or finished dietary supplements) that have been identified through a sound statistical sampling plan (i.e., reduced sampling), or for every batch of dietary supplements, the manufacturer must verify that the batch of dietary supplement meets product specifications for identity, purity, strength, and composition, and for limits on those types of contamination that may adulterate or that may lead to adulteration of the dietary supplement, applicable specific tests, performance, and manufacturing quality tests. To do so:

- One or more established specifications for identity, purity, strength, and composition, and the limits on those types of contamination that may adulterate or that may lead to adulteration of the dietary supplement, applicable specific tests, performance, and manufacturing quality tests, that if tested or examined on the batches of dietary supplement (i.e., reduced testing), would verify that the production process control system is producing a dietary supplement that meets all product specifications;
- Appropriate tests or examinations must be conducted to determine compliance with the applicable specifications;
- Adequate documentation must be provided on the basis for determining how compliance with the test specification(s) selected for reduced testing will ensure that the finished batch of dietary supplement will meet all product specifications for identity, purity, strength, and composition, and for the limits on those types of contamination that may adulterate or that may lead to adulteration of the dietary supplement, applicable specific tests, performance, and manufacturing quality tests; and
- Quality unit personnel must review and approve all supporting documentation for reduced testing.

3.2.5 RECEIVED IN-PROCESS (BULK) DIETARY SUPPLEMENT

Before packaging or labeling a dietary supplement received for packaging or labeling as a dietary supplement, for distribution rather than for return to the supplier, the product must be visually examined, and documentation must be provided or obtained through testing and examination to determine whether the in-process (bulk) product specifications are met.

3.2.6 PACKAGING MATERIAL AND LABELING

Before packaging material is used, at minimum, a visual identification of the containers and closures must be conducted, and the supplier's invoice, guarantee, or certification must be reviewed to determine whether the packaging specifications are met.

Before labeling is used, at minimum, a visual identification of the labeling must be conducted, and the supplier's invoice, guarantee, or certification must be reviewed to determine whether the labeling specifications are met.

3.2.7 FINISHED DIETARY SUPPLEMENTS

At minimum, a visual examination of the packaging and labeling of the finished packaged and labeled dietary supplement must be conducted to determine whether the packaging used and the label applied were specified in the master packaging control record.

3.2.8 DISPOSITION DECISION FOR MATERIALS

For components, in-process materials, packaging materials, labeling, and dietary supplements that meet specifications, the quality unit may approve the material for use in manufacturing.

For components, in-process materials, packaging materials, labeling, and dietary supplements that do not meet specifications, the quality unit must reject the material for use in manufacturing, unless quality unit personnel approve a treatment, an in-process adjustment, or reprocessing that will ensure the quality of the finished dietary supplement, and that the dietary supplement is packaged and labeled as specified in the master packaging record.

For components that do not meet specification(s) for identity (i.e., identification), quality control personnel must reject the component and the component must not be used in manufacturing the dietary supplement.

For a dietary supplement received from a supplier for packaging and/or labeling as a dietary supplement and for distribution rather than for return to the supplier that does not meet specifications, quality control personnel must reject the product and the product may not be packaged or labeled for distribution as a dietary supplement.

The quality unit personnel must not approve and release for distribution any batch or reprocessed batch of dietary supplement:

- For which any component in the batch does not meet its identity specification;
- That does not meet all product specifications;
- That has not been manufactured, packaged, labeled, and held under conditions to prevent adulteration; and
- That was received from a supplier for packaging or labeling as a dietary supplement, and for distribution rather than return to the supplier, for which sufficient assurance is not provided to adequately identify the product and to determine that the product is consistent with its purchase order.

3.2.9 TREATMENTS, IN-PROCESS ADJUSTMENTS, AND REPROCESSING

A rejected dietary supplement must not be reprocessed, and a rejected component or any component, packaging material, or labeling must not undergo treatment or in-process adjustment to make it suitable for use in the manufacture of a dietary supplement, unless:

- Quality unit personnel conduct a material review and make a disposition decision that is based on a scientifically valid reason and approves the reprocessing, treatment, or in-process adjustment;
- The reprocessing, treatment, or in-process adjustment will ensure the quality of the finished dietary supplement and that the dietary supplement is packaged and labeled as specified in the master manufacturing record; and
- All components in the batch met its identity (i.e., identification) specification.

For a rejected dietary supplement received from a supplier for packaging and/or labeling as a dietary supplement and for distribution rather than for return to the supplier that does not meet specifications, quality control personnel must reject the product and the product may not be packaged or labeled for distribution as a dietary supplement.

Any batch of dietary supplement that is reprocessed, that contains components that have been treated, or to which in-process adjustments have been made to make them suitable for use in the manufacture of the dietary supplement must be approved by quality unit personnel before release for distribution.

The quality unit personnel must not approve and release for distribution any batch or reprocessed batch of dietary supplement:

- For which any component in the batch does not meet its identity specification;
- That does not meet all product specifications;
- That has not been manufactured, packaged, labeled, and held under conditions to prevent adulteration; and
- That was received from a supplier for packaging or labeling as a dietary supplement, and for distribution rather than return to the supplier, for which sufficient assurance is not provided to adequately identify the product and to determine that the product is consistent with its purchase order.

3.3 Receiving and Release of Materials

3.3.1 COMPONENTS, PACKAGING MATERIALS, AND LABELS

The person responsible for receiving components, packaging, or labels should perform a visual inspection of each truck and examine the containers in the shipment that is received for appropriate content label, container damage, or broken seals to determine whether the container condition may have resulted in contamination or deterioration of the components, packaging materials, or labels. The correct temperature of all refrigerated trailers should be verified prior to unloading. The person must visually examine the supplier's invoice, guarantee, or certification in a shipment that is received to ensure the components, packaging materials, or labels are consistent with the purchase order.

The components, packaging materials, and labels must be placed in quarantine, either physically separated from approved goods or within integrated storage locations strictly controlled through a physical or electronic inventory system, before they are used in the manufacture of a dietary supplement until:

- Representative samples are collected of each unique shipment of components, packaging materials, and labels received, and of each unique lot within each unique shipment of components, packaging materials, and labels;

- Quality unit personnel review and approve the results of any tests or examinations conducted on components, packaging materials, and labels; and
- Quality unit personnel approves the components, packaging materials, and labels for use in the manufacture of a dietary supplement, including approval of any treatment or in-process adjustments of components, packaging materials, and labels to make them suitable for use in the manufacture of a dietary supplement, and releases them from quarantine.

Each unique lot within each unique shipment of components, packaging materials, and labels that is received, and any lot of components that are produced, must be identified in a manner that allows a person to trace the lot to the supplier; the date received; the name of the component, packaging material, and label; the status of the component, packaging material, and label (e.g., quarantined, approved, or rejected); and to the dietary supplement that was manufactured and distributed. This unique identifier must be used whenever recording the disposition of each unique lot within each unique shipment of components, packaging material, and labels that was received, and any lot of components produced.

Components, packaging material, and labels must be held under conditions that will protect against contamination and deterioration, and avoid mix-ups.

3.3.2 PRODUCT RECEIVED FOR PACKAGING AND LABELING AS A DIETARY SUPPLEMENT

The person responsible for receiving product that is received for packaging or labeling as a dietary supplement, and for distribution rather than for return to the supplier, must visually examine each immediate container or grouping of immediate containers in a shipment that is received for appropriate content label, container damage, or broken seals to determine whether the container condition may have resulted in contamination or deterioration of the received product. The person must visually examine the supplier's invoice, guarantee, or certification in a shipment of received product to ensure the received product is consistent with the purchase order.

The received product must be placed in quarantine before it is used in the packaging and labeling of a dietary supplement until:

- Representative samples are collected of each unique shipment of received product, and of each unique lot within each unique shipment of received product;
- Quality unit personnel review and approve results of any tests or examinations conducted on the received product, and review and approve the documentation supplied with the received product to determine whether the received product meets specifications; and
- Quality unit personnel approves the received product for packaging and labeling as a dietary supplement, and releases the received product from quarantine.

Each unique lot within each unique shipment of received product must be identified in a manner that allows a person to trace the lot to the supplier; the date received; the name of the received product, packaging material, and label; the status of the received product (e.g., quarantined, approved, or rejected); and to the dietary supplement that was packaged and labeled and distributed. This unique identifier must be used whenever recording the disposition of each unique lot within each unique shipment of received product.

Received product must be held under conditions that will protect against contamination and deterioration, and avoid mix-ups.

3.4 Representative Samples and Reserve Samples

3.4.1 REPRESENTATIVE SAMPLES

Quality unit personnel must collect representative samples:

- Of each unique shipment, and of each unique lot within each unique shipment, of components, packaging material, and labels to be used in manufacturing to determine whether the materials meet established specifications;
- Of in-process materials for each manufactured batch at points, steps, or stages in the manufacturing process as specified in the master manufacturing record where control is necessary to ensure identity, purity, strength, and composition of dietary supplements, to determine whether in-process materials meet specifications;
- Of each finished manufactured batch dietary supplement before releasing for distribution to verify that the finished batch of dietary supplement meets specifications;
- Of each unique shipment, and of each unique lot within each unique shipment, of product received for packaging or labeling as a dietary supplement and for distribution rather than for return to the supplier to determine whether the received product meets established specifications; and
- Of each lot of packaged and labeled dietary supplement to determine whether the packaging used and the label applied was specified in the master packaging control record.

Design of the sample room should be consistent with controls necessary to prevent cross-contamination.

Written procedures for sampling must be established and followed. The number of containers sampled, and the amount of material to be sampled from each container, should be based upon appropriate criteria such as component variability, statistical confidence levels, and degree of precision desired, the past quality history of the supplier, and the quantity of material needed for analysis and reserve, when required. Sampling procedures should include:

- Cleaning the containers of components selected for sampling prior to opening;
- Containers should be opened, sampled, and resealed in a manner designed to prevent contamination of their contents and contamination of other components, product containers, or closures; and
- Containers should be identified so that the following information can be determined: name of the material sampled, the lot number, the container from which the sample was taken, the date on which the sample was taken, and the name of the person who collected the sample.

Sampling of botanicals should be in compliance with the provisions in ⟨561⟩.

3.4.2 RESERVE SAMPLES

Quality unit personnel must collect and hold reserve samples:

- Of each lot of packaged and labeled dietary supplements that is distributed, which must be held using the same container-closure system in which the packaged and labeled dietary supplement is distributed;
- Of each lot of dietary supplement that is being distributed to be packaged and labeled, which must be held using a container-closure system that provides essentially the same characteristics to protect against contamination or deterioration as the one in which it is distributed for packaging and labeling elsewhere.

Reserve samples of dietary supplements must be identified with the batch, lot, or control number. The reserve sample of each batch of dietary supplements must consist of at least twice the quantity necessary for all tests or examinations to determine whether or not the dietary supplement meets product specifications, and must be collected and retained for at least one (1) year past its shelf life (expiry) date.

3.5 Holding, Distribution, and Transportation

Written procedures must be established and followed for holding or warehousing and distributing operations.

3.5.1 HOLDING

Components and dietary supplements must be held under appropriate conditions of temperature, humidity, and light so that the identity, purity, strength, and composition of the components and dietary supplements are not affected. Temperature and humidity of each warehouse must be monitored and should be mapped where appropriate during both the summer and winter to ensure that required storage conditions are controlled and documented. Packaging materials and labeling must be held under appropriate conditions so that the packaging materials and labeling are not adversely affected. Components, dietary supplements, packaging materials, and labeling must be held under conditions that do not lead to the mix-up or contamination of components, dietary supplements, packaging materials, and labeling.

In-process material must be identified and held under appropriate conditions that protect against mix-up and contamination. In-process material must be held under appropriate conditions of temperature, humidity, and light to protect against deterioration.

Components, in-process materials that contain food allergens must be clearly identified and held in a manner that prevents allergen cross-contact.

Spills of allergen-containing components must be cleaned promptly and assessed to determine the potential for cross-contamination to adjacent materials.

Reserve samples of dietary supplements must be held in a manner that protects against contamination and deterioration. Reserve samples of dietary supplements must be held under conditions consistent with the label conditions stated on the product labels, or if no storage conditions are recommended on the label [e.g., for in-process (bulk) dietary supplements], under ordinary storage conditions consistent with expected storage conditions for the finished product while on display at retail. Reserve samples of dietary supplements must be held using the same container-closure system in which packaged and labeled dietary supplements are distributed, or if distributing dietary supplements to be packaged and labeled, using a container-closure system that provides essentially the same characteristics to protect against contamination or deterioration as the one in which dietary supplements will be distributed.

Reserve samples must be retained for one (1) year past the shelf life (expiry) date of the dietary supplement for use in appropriate investigations.

3.5.2 REJECTED MATERIALS

Any component, packaging material, labels, and product received for packaging and labeling as a dietary supplement and for distribution rather than return to the supplier that is rejected and is unsuitable for use in manufacturing, packaging, and labeling operations, must be clearly identified, held, and controlled under a quarantine system for appropriate disposition. The quarantine system for rejected materials must include physical segregation and conspicuous labeling of the material in addition to electronic controls.

3.5.3 RETURNED DIETARY SUPPLEMENTS

Returned dietary supplements must be identified and quarantined until quality unit personnel conduct a material review and make a disposition decision.

Returned dietary supplements must be destroyed, or otherwise suitably disposed of, unless the outcome of a material review and disposition decision is that quality control personnel do the following:

- Approve the salvage of the returned dietary supplement for redistribution; or
- Approve the returned dietary supplement for reprocessing.

A returned dietary supplement may be salvaged only if quality control personnel conduct a material review and make a disposition decision to allow the salvage.

Any returned dietary supplements that are reprocessed must meet all in-process (bulk) dietary supplement specifications, and quality control personnel must approve or reject the release for distribution any returned dietary supplement that is reprocessed.

If the reason for a dietary supplement being returned implicates other batches, an investigation must be conducted of the manufacturing processes and each of those other batches to determine compliance with specifications.

3.5.4 DISTRIBUTION

Dietary supplements must be distributed under conditions that will protect the dietary supplement against contamination and deterioration. Distributing operations must be designed to facilitate recall of the dietary supplement, if necessary.

3.5.5 TRANSPORTATION OPERATIONS

All transportation operations must be conducted under such conditions and controls necessary to prevent dietary supplements from becoming spoiled or adulterated during transportation.

Vehicles and transportation equipment used in transportation operations must be:

- Designed and maintained, and equipped as necessary to provide adequate temperature control to prevent components and dietary supplements requiring temperature control (e.g., chewable gels, soft gelatin capsules) from becoming spoiled during transportation; and
- Stored in a manner that prevents it from harboring pests or becoming contaminated in any other manner that could result in components or dietary supplements for which it will be used becoming adulterated during transportation operations.

Responsibility for ensuring that transportation operations are carried out adequately must be assigned to competent supervisory personnel.

Shippers, receivers, loaders, and carriers engaged in transportation must conduct all transportation operations under such conditions and controls necessary to prevent components and dietary supplements from becoming unsafe during transportation. Such operations include taking effective measures:

- Such as segregation, isolation, or the use of packaging to protect components and dietary supplements from contamination from other articles in the same load;
- To ensure that components and dietary supplements that requires temperature control for safety and quality are transported under adequate temperature control; and
- Restricting the co-shipment of non-food items that might render the components or finished dietary supplements adulterated through cross-contamination.

Shippers must specify to the carrier and the loader all necessary sanitary specifications for the carrier's vehicle and transportation equipment including any specific design specifications (e.g. temperature control) and cleaning procedures.

Loaders must determine, considering as appropriate specifications provided by the shipper, that the vehicle or transportation equipment is in appropriate sanitary and operational condition for the transport of components and dietary supplements.

Receivers, upon receipt of components and dietary supplements, must take steps to adequately assess that the components and dietary supplements were not subjected to adverse conditions that may have caused them to become adulterated.

Carriers must ensure that vehicles and transportation equipment meet the shipper’s specifications and are otherwise appropriate to prevent components and dietary supplements from becoming adulterated during transportation operations.

Measures to implement requirements and procedures may be accomplished by the shipper or the carrier or another party involved in transportation operations under a written agreement.

Records should be maintained regarding specifications, agreements, procedures, associated records related to transportation (maintenance, cleaning, previous cargoes, temperature control), and training.

3.6 Quality Unit Responsibilities for Materials Management Operations

Before components, packaging materials, and labeling are used in manufacturing, quality unit personnel must:

- Review all receiving records for components, packaging, and labeling;
- Determine whether all components, packaging, and labeling conformed to established specifications;
- Conduct any required material review and make any required disposition decision;
- Approve or reject any treatment and in-process adjustments of components, in-process materials, packaging, or labeling to make them suitable for use in the manufacture of a dietary supplement; and
- Approve, and release from quarantine, all components, packaging, and labeling before they are used in manufacturing.

For returned dietary supplements, quality unit personnel must:

- Conduct any required material review and make any required disposition decision, including determining whether tests or examinations are necessary to determine compliance with established product specifications, and review the results of any tests or examinations that are conducted to determine compliance with established product specifications;
- Approve or reject any salvage and redistribution of any returned dietary supplements;
- Approve or reject any reprocessing of any returned dietary supplement; and
- Determine whether the reprocessed dietary supplement meets product specifications and either approve for release, or reject, any returned dietary supplement that is reprocessed.

3.7 Materials Management Operations and Controls Documentation

The following documentation must be made and kept for fulfilling the requirements of the Material Management Controls System (quality system 3).

3.7.1 WRITTEN PROCEDURES

Written procedures must be established and followed for materials management operations and controls, including:

- Preparing, reviewing, and approving material and in-process production specifications;
- Material receiving, sampling, testing, and making a disposition decision for materials to be used in manufacturing;
- Warehousing maintenance, cleaning, and inventory controls;
- Pallet inspection, cleaning, and maintenance;
- Implementing a supplier qualification program;
- Holding and distributing operations;
- Receiving and conducting material reviews and making disposition decisions for returned dietary supplements.

3.7.2 RECORDS

Records must be made and kept for:

- Specifications for components, in-process production, packaging materials, labeling, in-process (bulk) dietary supplements, received in-process (bulk) dietary supplements, and finished dietary supplements;
- List of approved suppliers of components, packaging materials and labeling, and corresponding supplier qualification evaluation reports for the purpose of relying on the supplier's certificate of analysis;
- Documentation for why meeting in-process specifications, in combination with meeting component specifications, helps to ensure the dietary supplement meets the specifications for identity, purity, strength, and composition, and for limits on those types of contamination that may adulterate or may lead to adulteration of the finished batch of the dietary supplement;
- Documentation that justifies why a reduced testing program is appropriate;
- Receiving records (including, certificates of analysis, supplier's invoice, and supplier's guarantee) for components, packaging, and labels, and for products received for packaging or labeling as a dietary supplement, and for distribution rather than for return to the supplier;
- Documentation by the person who performs the required operation, at the time of performance, that the required operation was performed, including:
    - The date that the components, packaging, labeling, or products received for packaging or labeling as a dietary supplement were received;
    - The initials of the person performing the required operation;
    - The results of any tests or examinations conducted on components, packaging, or labeling, and of any visual examination of product received for packaging or labeling as a dietary supplement; and
    - Any material review and disposition decision conducted on components, packaging material, labeling, or products received for packaging and labeling as a dietary supplement;
- Inventory control records documenting material history of use;
- Documentation, at the time of performance, demonstrating that quality control unit personnel determined whether the specifications set for materials to be used in manufacturing were met (i.e., performed the required tests and made a disposition decision for materials);
- Dietary supplement distribution;
- Documentation of any material review and disposition decisions on a returned dietary supplement;
- The results of any testing or examination of returned dietary supplements to determine compliance with product specifications; and
- Documentation of the reevaluation by quality unit personnel of any dietary supplement that is reprocessed and the determination by quality unit personnel of whether the reprocessed dietary supplement meets in-process (bulk) dietary supplement specifications.

4. PRODUCTION OPERATIONS AND CONTROLS

4.1 Master Manufacturing Records

Written master manufacturing records must be prepared and followed for each unique formulation of dietary supplements manufactured, and for each batch size, to ensure uniformity in the finished batch from batch to batch.

The master manufacturing record may include all manufacturing, packaging, and labeling directions and controls, or be separated into two records: one for manufacturing and another for packaging and labeling. In some cases, such as in soft gelatin product manufacturing, the gelatin manufacturing record may be separated from that of the fill material used to make a specific final product lot.

The master manufacturing record must:

- Identify in-process production specifications for the points, steps, or stages in the manufacturing process where control is necessary to ensure the quality of the dietary supplement and that the dietary supplement is packaged and labeled as specified in the master manufacturing record; and
- Establish controls and procedures to ensure that each batch of dietary supplement that is manufactured meets in-process specifications.

The batch production record must include:

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

- A complete list of components to be used;
- An accurate statement of the weight or measure of each component to be used;
- Any necessary weight or measure adjustment due to actual strength or purity of the dietary ingredients with labeled dietary supplements claims;
- The identity and weight or measure of each dietary ingredient that will be declared on the supplement facts label and the identity of each ingredient that will be declared on the ingredients list of the dietary supplement;
- A statement of any intentional overage amount of a dietary ingredient;
- A statement of theoretical yield of a manufactured dietary supplement expected at each point, step, or stage of the manufacturing process where control is needed to ensure the quality of the dietary supplement, and the expected yield at the end of manufacturing the dietary supplement, including the maximum and minimum percentages of theoretical yield beyond which a deviation investigation of a batch is necessary and material review is conducted and disposition is made; and a description of packaging and a representative label, or cross-reference to the physical location of the actual or representative label.

The master manufacturing record must also include written instructions, including the following:

- Specifications for each point, step, or stage in the manufacturing process where control is necessary to ensure the quality of the dietary supplement and that the dietary supplement is packaged and labeled as specified in the master manufacturing record;
- Procedures for sampling and cross-reference to procedures for tests and examinations;
- Specific actions necessary to perform and verify points, steps, or stages in the manufacturing process where control is necessary to ensure the quality of the dietary supplement and that the dietary supplement is packaged and labeled as specified in the master manufacturing record:
    - Such specific actions must include verifying the weight or measure of any component and verifying the addition of any component; and
    - For manual operations, such specific actions must include:
        - One person weighing or measuring a component and another person verifying the weight or measure; and
        - One person adding the component and another person verifying the addition;
- Special notations and precautions to be followed; and
- Corrective action plans for use when a specification is not met.

Detailed production instructions should also include:

- Sequences to be followed;
- Ranges of process parameters to be used;
- Time limits for completion of individual processing steps or the total process, where appropriate.

The dietary supplement must be formulated with the intent to provide 100% of the quantitative label amount of each dietary ingredient and may include overage inputs as necessary to ensure the product meets label claim at the end of shelf life. The contents of the declared dietary ingredients and/or their marker compounds must be consistent with the strengths stated on the label within the tolerances established as acceptance criteria set in the specifications and the local regulatory requirements.

4.2 Executed Batch Production Records

An executed batch production record must be prepared every time a batch of dietary supplements is manufactured, and it must include complete information relating to the production and control of each batch. The executed batch production record must accurately follow the appropriate master manufacturing record and each step in the production of the batch must be performed.

The executed batch production record must include:

- The batch, lot, or control number of the dietary supplement; of each lot of packaged and labeled dietary supplement from a finished batch of dietary supplement; and each lot of dietary supplement, from the finished batch of dietary supplement, that is distributed to another person for packaging or labeling;
- The identity of equipment and processing lines used in producing the batch;
- The date and time of the maintenance, cleaning, and sanitizing of the equipment and processing lines used in producing the batch, or a cross-reference to records, such as individual equipment logs, where this information is retained;
- The unique identifier that was assigned to each component, or, when applicable, to a product that was received from a supplier for packaging and labeling as a dietary supplement, packaging and label used;
- The identity and weight or measure of each component used;
- A statement of the actual yield and a statement of the percentage of theoretical yield at appropriate phases of processing;
- The actual results obtained during any monitoring operation;
- The results of any testing or examination performed during the batch production, or a cross-reference to such results;
- Documentation that the finished dietary supplement meets the in-process (bulk) dietary supplement and finished dietary supplement specifications.

The executed batch production record must also include documentation, at the time of performance, of the manufacture of the batch, including:

- The date on which each step of the master manufacturing record was performed;

- The initials of the person performing each step, including initials of the person responsible for:
  - Weighing or measuring each component used in the batch;
  - Verifying the weight or measure of each component used in the batch;
  - Adding the component to the batch; and
  - Verifying the addition of components to the batch;
- Documentation, at the time of performance, of packaging and labeling operations, including:
  - The unique identifier that was assigned to packaging and labels used, the quantity of the packaging and labels used, and, when label reconciliation is required, reconciliation of any discrepancies between issuance and use of labels;
  - An actual or representative label, or a cross-reference to the physical location of the actual or representative label specified in the master manufacturing (or packaging and labeling) record; and
  - The results of any tests or examinations conducted on packaged and labeled dietary supplements, including repackaged or relabeled dietary supplements, or a cross-reference to the physical location of such results;

- Documentation at the time of performance that quality unit personnel:
  - Reviewed the batch production record, including review of any monitoring operation required for determining compliance to material specifications, and review of the results of any tests and examinations, including tests and examinations conducted on components, in-process materials, finished batches of dietary supplements, and packaged and labeled dietary supplements;
  - Approved or rejected any reprocessing or repackaging;
  - Approved and released, or rejected, the batch for distribution, including any reprocessed batch;
  - Approved and released, or rejected, the packaged and labeled dietary supplement, including any repackaged or relabeled dietary supplement;

- Documentation at the time of performance or any required material review and disposition decision; and
- Documentation at the time of performance of any reprocessing.

4.3 Manufacturing Operations Production and Process Controls

Written procedures must be established and followed for manufacturing operations. Manufacturing processes must be designed and selected to ensure that dietary supplement specifications are consistently met.

All manufacturing operations must be conducted in accordance with adequate sanitation principles.

All necessary precautions must be taken during the manufacture of a dietary supplement to prevent contamination of components or dietary supplements. These precautions include:

- Performing manufacturing operations under conditions and controls that protect against the potential for growth of microorganisms; the potential for allergen cross-contact and contamination; and the potential for the adulteration of raw materials, in-process materials, and finished product;
- Washing and cleaning components that contain soil and other contaminants;
- Using water that, at a minimum, complies with the applicable federal, state, and local requirements and does not contaminate the dietary supplement when the water may become a component of the finished batch of dietary supplement;
- Performing chemical, microbiological, or other testing, as necessary to prevent the use of contaminated components;
- Sterilizing, pasteurizing, freezing, refrigerating, controlling hydrogen-ion concentration (pH), controlling humidity, controlling water activity (a_w), or using any other effective means to remove, destroy, or prevent the growth of microorganisms and prevent decomposition;
- Holding components and dietary supplements that can support the rapid growth of microorganisms of public health significance in a manner that prevents the components and dietary supplements from becoming adulterated;
- Identifying and holding any components or dietary supplements, for which a material review and disposition decision is required, in a manner that protects components or dietary supplements that are not under a material review against contamination and mix-up with those that are under a material review;
- Performing mechanical manufacturing steps (such as cutting, sorting, inspecting, shredding, drying, grinding, blending, and sifting) by any effective means to protect the dietary supplements against contamination by, for example:
  - Cleaning and sanitizing contact surfaces;
  - Using temperature controls; and
  - Using time controls;

- Using effective measures to protect against the inclusion of metal or other foreign material in components or dietary supplements, by, for example, filters or strainers, traps, magnets, or electronic metal detectors;
- Segregating and identifying all containers for a specific batch of dietary supplements to identify their contents and, when necessary, the phase of manufacturing; and
- Identifying all processing lines and major equipment used during manufacturing to indicate their contents, including the name of the dietary supplement and the specific batch or lot number and, when necessary, the phase of manufacturing.

4.4 Quality Unit Responsibilities for Production

Quality unit personnel must:

- Review and approve all master manufacturing records (MMR) and all modifications to them;
- Review and approve all master packaging and labeling records (if separate from the MMR) and all modifications to them;
- Review and approve all batch production-related records;
- Review all monitoring required for determining compliance to material specifications;
- Conduct any material review and make any required disposition decisions;
- Approve or reject any treatments, in-process adjustments, and reprocessing;
- Determine whether all in-process production specifications are met;
- Determine whether each finished batch of dietary supplements conforms to its specifications; and
- Make a disposition decision (approving and releasing, or rejecting) each finished batch of dietary supplements, including any reprocessed finished batch of dietary supplements, for distribution.

4.5 Disposition Decision for Production

For supplements that meet specifications and that were manufactured, packaged, labeled, and held under conditions to ensure the quality of the dietary supplement, the quality unit may approve and release the batch of dietary supplements for distribution.

The quality unit personnel must not approve and release for distribution any batch or reprocessed batch of dietary supplement:

- For which any component in the batch does not meet its identity specification;
- That does not meet all product specifications;
- That has not been manufactured, packaged, labeled, and held under conditions to prevent adulteration; and
- That was received from a supplier for packaging or labeling as a dietary supplement, and for distribution rather than return to the supplier, for which sufficient assurance is not provided to adequately identify the product and to determine that the product is consistent with its purchase order.

4.6 Production Operations and Controls Documentation

The following documentation must be made and kept for fulfilling the requirements of the Production Operations and Controls System (quality system 4).

4.6.1 WRITTEN PROCEDURES

Written procedures for manufacturing operations must be established and followed for:

- Preparing and approving master manufacturing records and production instructions;
- Cleaning and inspecting manufacturing facilities;
- Conducting manufacturing production operations; and
- Quality unit responsibilities and operations.

4.6.2 RECORDS

Records must be made and kept for manufacturing operations, including:

- Master manufacturing records and executed batch production records;
- Equipment and production suite cleaning records; and
- Documentation of any material reviews and disposition decisions by the quality unit.

5. PACKAGING AND LABELING OPERATIONS AND CONTROLS

5.1 General

There must be written procedures designed to ensure that correct packaging materials and labels are used. Packaging and labeling operations must be designed to prevent mix-ups.

There should be written procedures describing the receipt, identification, quarantine, sampling, examination and/or testing and release, and handling of packaging and labeling materials.

Packaging and labeling material should conform to established specifications. Those that do not comply with such specifications should be rejected to prevent their use in operations for which they are unsuitable.

Records should be maintained for each shipment of labels and packaging materials showing receipt, examination or testing, and whether accepted or rejected.

5.2 Packaging Materials

5.2.1 GENERAL

Necessary actions must be taken to determine whether packaging for dietary supplements meets specifications so that the condition of the packaging will ensure the quality of the dietary supplements [cGMP, 21 CFR §111.410(a)]. Containers must provide adequate protection against deterioration or contamination of the dietary supplement that may occur during transportation and recommended storage.

Chapter ⟨659⟩ provides packaging definitions, auxiliary packaging information, and storage condition definitions relevant to the storage and distribution of dietary supplements, and should be consulted.

Containers must be clean and, where indicated by the nature of the product, sanitized to ensure that they are suitable for their intended use. These containers must not be reactive, additive, or absorptive so as to alter the quality of the dietary supplement beyond specified limits.

If containers (e.g., for components, in-process materials, or bulk material) are re-used, they should be cleaned in accordance with documented procedures and all previous labels should be removed or defaced.

5.2.2 TAMPER-RESISTANT PACKAGING

Dietary supplements for retail sale must be packaged in a tamper-resistant package. A tamper-resistant package is one having an indicator or barrier to entry which, if breached or missing, can reasonably be expected to provide visible evidence to consumers that tampering has occurred. To reduce the likelihood of substitution of a tamper-resistant feature after tampering, the indicator or barrier to entry must be distinctive by design or by the use of an identifying characteristic (e.g., a pattern, name, registered trademark, logo, or picture). The term “distinctive by design” means that the packaging cannot be duplicated with commonly available materials or through commonly available processes. A tamper-resistant package may involve a primary container–closure system, a secondary container or carton system, or any combination of systems intended to provide a visual indication of package integrity. The tamper-resistant feature should be designed to remain intact when handled in a reasonable manner during manufacture and distribution, or held at retail display.

5.3 Labeling

5.3.1 GENERAL

Labeling must comply with applicable federal and state labeling regulations or dietary supplements.

Quantitative label claims for the product must be truthful and accurately reflect the contents of the declared dietary ingredients and/or their marker compounds.

Reference to the *USP–NF* on the label or labeling must be appropriate and completely accurate in accordance with the *General Notices, 3.20 Indicating Conformance*. When the dietary supplement product monograph title appears on the label, the product must fully conform to the specified compendial standard.

Labeling must comply with applicable labeling regulations for dietary supplements, including, but not limited to, listing:

- The term “dietary supplement” or “supplement”;
- The quantity of each dietary ingredient and the correct reference daily intake, listed as percent daily value, as necessary;
- The common or usual name of each ingredient in descending order of predominance by weight, except that dietary ingredients listed in the nutrition label supplement facts need not be repeated in the ingredient list; incidental additives including water, present in a dietary supplement at insignificant levels are exempted from this requirement;
- With respect to a proprietary blend of ingredients, the total quantity of all ingredients in the blend is provided in order of predominance by weight and identified by the term “proprietary blend” or other appropriately descriptive term;
- Products making a claim of health benefit (including statements, symbols, or vignettes) do so in a manner that is consistent with the applicable regulatory requirements; health benefit claims include structure/function claims, health claims, and qualified health claims.

For botanicals, the common or usual name and/or the Latin binomial of the botanical species must be listed on the label. The American Herbal Product Association’s publication, *Herbs of Commerce*, current edition, should be consulted regarding the appropriate common or usual name of a botanical ingredient. Additionally, the proper Latin binomial name should be provided in parenthesis on the label, except that this name is not required when it is synonymous with the common or usual name for the botanical species. The label must include the plant part(s) used. The terms "whole", "root", "seed", "aerial", and "leaf" are all acceptable terminology.

Labels for dietary supplements containing iron or iron salts for use as an iron source must include the following required cautionary statement: “WARNING: Accidental overdose of iron-containing products is a leading cause of fatal poisoning in children under 6. Keep this product out of reach of children. In case of accidental overdose, call a doctor or poison control center immediately.”

Dietary supplements that contain over 250 mg of elemental iron in a single package must comply with the Consumer Product Safety Commission’s regulations for child resistant packaging.

Labeling for dietary supplements must comply with applicable allergen labeling requirements as promulgated in the Food Allergen Labeling and Consumer Protection Act (FALCPA).

The label must include a statement of the necessary storage requirements for the dietary supplement.

The label must accurately state the country of origin for any product of foreign origin imported into the United States.

The name and place (city, state, zip code) of business of the manufacturer, packer, or distributor must be located to the right of the principle display panel. When the name appearing on the label is not that of the actual manufacturer, the name should be qualified in a manner to accurately reflect this relationship (e.g., “Manufactured for ___”, “Distributed by ___”). The label must include a domestic address or phone number through which an adverse event report for a dietary supplement may be received.

5.3.2 SHELF LIFE (EXPIRY) DATE

Dietary supplement labeling must state a shelf life (expiry) date that is indicative of the date before which the dietary supplement is ensured to meet applicable specifications of identity, strength, quality, and purity when stored under labeled conditions. The shelf life (expiry) date must be supported by suitable stability data.

There must be a written procedure designed to ensure that the correct shelf life (expiry) date is printed on the finished dietary supplement labeling.

5.3.3 TAMPER-RESISTANT LABELING

Each retail package of a dietary supplement covered by this section must bear a statement that is prominently placed so that consumers are alerted to the specific tamper-resistant feature of the package. The labeling statement should be so placed that it will be unaffected if the tamper-resistant feature of the packaging is breached or missing. If the tamper-resistant feature chosen to meet the requirement above is one that uses an identifying characteristic, that characteristic should be referred to in the labeling statement. For example, the labeling statement on a bottle with a shrink band could say “For your protection, this bottle has an imprinted seal around the neck.”

5.4 Labeling Issuance and Control

Access to the label storage areas (i.e., label control room) must be limited to authorized personnel. Procedures for labeling issuance and control should be established to ensure that labels are stored in a manner that prevents mix-ups and provides proper identification used to reconcile the quantities of labels issued, used, and returned, and to evaluate discrepancies found between the number of containers labeled and the number of labels issued and used. Such discrepancies should be investigated, and the investigation should be approved by the quality unit(s).

All excess labels bearing batch numbers or other batch-related printing should be destroyed. Returned labels should be maintained. Obsolete and outdated labels, and incorrect labels should be destroyed to ensure that they are not used in any future packaging and labeling operations.

Printing devices used to print labels for packaging operations (e.g., for bulk packaging) should be controlled to ensure that all imprinting conforms to the print specified in the batch production record.

Labeling issuance must be designed to prevent mix-ups. Strict control must be exercised over issuance of labeling for use in finished dietary supplement labeling operations. Labels should be delivered to packaging lines in a secured container (e.g., locked box or cage).

Labeling materials issued for a batch should be carefully examined for proper identity and conformity to the labeling specifications in the batch packaging record. A printed label or copy of the printed label representative of those used must be included in the batch packaging record.

Procedures should be used to reconcile the quantities of labeling issued, used, and returned, and should require evaluation of discrepancies found. If discrepancies are found between the quantity of product finished and the quantity of labeling issued and are outside preset limits based on historical operating data, such discrepancies should be investigated.

If a 100-percent examination for correct labels has been performed by appropriate electronic or electromechanical equipment during or after completion of finishing operations, then label reconciliation is not required for cut or rolled labels.

Returned labeling should be maintained and sorted in a manner to prevent mix-ups and provide proper identification. All excess labeling bearing lot or control numbers should be destroyed and documented.

5.5 Packaging and Labeling Operations

Filling, assembling, packaging, labeling, and other related operations must be performed in a manner that ensures the quality of the dietary supplement, and that the dietary supplement is packaged and labeled as specified in the master packaging record. This must be done using any effective mean including the following:

- Cleaning and sanitizing all filling and packaging equipment, utensils, and dietary supplement packaging, as appropriate;
- Protecting manufactured dietary supplements from contamination, particularly airborne contamination;
- Using sanitary handling procedures;
- Establishing physical or spatial separation of packaging and labeling operations from operations on other components and dietary supplements to prevent mix-ups;
- Identifying, by any effective means, filled dietary supplement containers that are set aside and held in unlabeled conditions for future label operations, to prevent mix-ups;
- Assigning a batch, lot, or control number to each lot of packaged and labeled dietary supplement from a finished batch of dietary supplement; and each lot of dietary supplement, that you distribute to another person for packaging or labeling;
- Examining a representative sample of each batch of the packaged and labeled dietary supplement to determine whether the finished dietary supplement meets its specifications; and
- Suitably disposing of labels and packaging for dietary supplements that are obsolete or incorrect to ensure that they are not used in any future packaging and labeling operations.

There must be written procedures designed to ensure that correct packaging materials and labeling are used. Issuance and use of packaging and labels and reconciliation of any issuance and use discrepancies must be controlled. Before packaging and labeling operations begin, packaging and labeling for each batch of dietary supplements must be examined to determine whether the packaging and labeling conforms to the batch packaging control record. Packaging and labeling materials must be identified by item control number and lot number.

Packaging and labeling facilities must be inspected immediately before use to ensure that all materials not needed for the next packaging operation have been removed, and that packaging and labeling facilities have been properly cleaned. Results of the inspection and cleaning should be documented in the batch packaging control records, the packaging facility log, or other documentation system.

Packaged and labeled dietary supplements should be examined to ensure that containers and packages in the batch have the correct label. This examination should be part of the packaging operation. Results of these examinations must be recorded in the batch packaging control record.

A reserve sample of each batch of finished dietary supplements, consisting of at least twice the quantity necessary for finished dietary supplement specification tests and examinations, must be collected and retained for at least one (1) year past its shelf life (expiry) date.

In-process dietary supplements that are transported outside the manufacturer's control must be sealed in a manner such that, if the seal is breached or missing, the recipient will be alerted to the possibility that the contents may have been altered.

Any packaged and labeled dietary supplement that is rejected for distribution must be clearly identified, held, and controlled under a quarantine system for appropriate disposition.

The complete manufacturing history and control of the packaged and labeled dietary supplement through distribution must be traceable.

5.6 Repackaging and Relabeling

Dietary supplements may be repackaged or relabeled only after quality unit personnel have approved such repackaging or relabeling. A representative sample of each batch of repackaged or relabeled dietary supplements must be examined to determine whether the repackaged or relabeled dietary supplements meet all established specifications. Quality unit personnel must approve or reject each batch of repackaged or relabeled dietary supplements prior to its release for distribution.

Good Repackaging Practices ⟨1178⟩ should be consulted.

5.7 Quality Unit Responsibilities for Packaging and Labeling Operations

For packaging and labeling operations, quality unit personnel must:

- Review the results of any visual examination and documentation to ensure that specifications for product received from a supplier, for packaging and labeling as a return to the supplier, is met;
- Approve, and release from quarantine, all products received for packaging and labeling as a dietary supplement, and for distribution rather than for return to the supplier, before they are used for packaging and labeling;
- Review and approve all records for packaging and labeling operations;
- Determine whether the finished packaged and labeled dietary supplement conforms to established specifications;
- Conduct any required material review and make any required disposition decisions;
- Approve or reject any repackaging of a packaged dietary supplement;
- Approve or reject any relabeling of a packaged and labeled dietary supplement; and
- Approve for release, or reject, any packaged and labeled dietary supplement, including repackaged or relabeled dietary supplements, for distribution.

5.8 Packaging and Labeling Operations and Controls Documentation

The following documentation must be made and kept for fulfilling the requirements of the Packaging and Labeling Operations and Controls System (quality system 5).

5.8.1 WRITTEN PROCEDURES

Written procedures for packaging and labeling operations must be established and followed for:

- Receipt, identification, quarantine, sampling, examination and/or testing and release, and handling of packaging and labeling materials;
- Preparation and approval of packaging material and labeling specifications;
- Preparation and approval and master batch packaging and labeling control records;
- Cleaning and inspecting packaging and labeling facilities;
- Filling, assembling, packaging, labeling, and other related operations; and
- Determination and issuance of finished dietary supplement shelf-life (expiry) date to batch packaging and labeling control records.

5.8.2 RECORDS

Records for packaging and labeling must be made and kept for:

- Packaging and labeling specifications;
- Packaging and labeling facility cleaning and inspection records;
- Executed batch packaging and labeling control records; and
- Executed batch repackaging and relabeling control records.

6. LABORATORY OPERATIONS AND CONTROLS

6.1 General

Written procedures must be established and followed for laboratory operations, including written procedures for the tests and examinations to be conducted to determine whether specifications are met.

Adequate laboratory facilities must be used for whatever testing or examinations are necessary to determine whether components, packaging materials, labeling, in-process materials, and dietary supplements meet specifications.

Laboratory control processes must be established and followed that are reviewed and approved by quality unit personnel, including the following:

- Criteria to be used for establishing appropriate specifications;
- Sampling plans for obtaining representative samples of:
    - Components, packing materials, and labels;
    - In-process materials;

- Finished batches of dietary supplements;
- Product that is received for packaging or labeling as a dietary supplement, and for distribution rather than for return to the supplier; and
- Packaged and labeled dietary supplements;

- Use of criteria for selecting appropriate examination and testing methods;
- Use of criteria for selecting standard reference materials used in performing tests and examinations; and
- Use of test methods and examinations in accordance with established criteria.

Quality control personnel must verify that the laboratory examination and testing methodologies are appropriate for their intended use. Quality control personnel must identify and use appropriate scientifically validated methods for each established specification for which testing or examination is required to determine whether the specification is met.

Specifications, sampling plans, and test procedures, including changes or modifications to them, should be drafted by the appropriate quality control unit personnel and reviewed and approved by the appropriate quality assurance unit personnel. Specifications should be established in accordance with accepted standards and consistent with the manufacturing process.

There must be documented procedures describing sampling, testing, approval and rejection of materials, and recording and storage of laboratory data.

6.2 Reagents and Reference Standards

Reagents and standard solutions should be prepared and labeled following written procedures. “Use by” dates should be established and applied as appropriate for analytical reagents and standard solutions.

Primary reference standards should be obtained as appropriate for the manufacture of dietary supplements. The source of each primary reference standard must be documented. Records should be maintained of each primary reference standard’s storage and use in accordance with the supplier’s recommendations. Primary reference standards obtained from an officially recognized source, e.g., USP Reference Standards, may be used without testing if stored under conditions consistent with the supplier’s recommendations.

Where a primary reference standard is not available from an officially recognized source, an “in-house primary standard” must be established. Appropriate testing needs to be performed to establish fully the identity and purity of the “in-house primary reference standard”. Appropriate documentation of this testing should be maintained.

Secondary reference standards should be appropriately prepared, identified, tested, approved, and stored. The suitability of each batch of secondary reference standard should be determined prior to first use by comparing against a primary reference standard. Each batch of secondary reference standards should be periodically requalified in accordance with a written protocol.

6.3 Scientifically Validated Test Procedures

Tests and examinations that are used to determine whether material specifications are met must be scientifically validated methods, and appropriate for their intended use. Tests methods or procedures must meet proper standards of accuracy and reliability.

6.3.1 Validation of Test Procedures

If the test procedure is not in an official compendium, the procedure must be validated according to ⟨1225⟩. Method performance characteristics include specificity, linearity, range accuracy, precision, detection limit, and quantitation limit, and those of interest may vary depending on the type of test: identification, assay, impurities, or performance.

For microbial test procedures, the following *USP* general chapters should be consulted:

- *Biological Assay Validation* ⟨1033⟩
- *Validation of Alternative Microbiological Methods* ⟨1223⟩
- *Validation of Microbial Recovery from Pharmacopeial Articles* ⟨1227⟩

For performance test procedures, the following *USP* general chapter should be consulted:

- *The Dissolution Procedure: Development and Validation* ⟨1092⟩

6.3.2 Verification of Official Test Procedures

If the test procedure is in an official compendium, such as *USP–NF* or AOAC International *Official Methods of Analysis*, the procedure only needs to be verified for its suitability under actual conditions of use, according to *Verification of Compendial Procedures* ⟨1226⟩. Verification requirements should be based on an assessment of the complexity of both the procedure and the material to which the procedure is applied. Verification is not required for basic compendial procedures, such as loss on drying, residue on ignition, and simple instrumental determinations, such as pH measurements.

6.4 Test Procedures

Test procedures must have clear, complete descriptions, so as to provide an analyst with directions on how to reproducibly perform the given test. Test procedures should include the following information, as applicable:

- Purpose;
- Safety information, if applicable;
- Materials and equipment;
- Procedure, as applicable:
  - System suitability;

- Preparation of solutions and reagents;
- Preparation of standards and samples;
- Instrumental parameters; and
- Calculations and reporting;

- Review and approval with approval dates;
- Revision history.

The tests and examinations can include gross organoleptic analyses, macroscopic analyses, microscopic analyses, chemical (inorganic and organic) analyses, microbiological analyses, DNA-based analyses, and other scientifically valid methods.

Test procedures should be followed and documented at the time of performance, and any departure from established test procedures should be documented and explained.

All validated procedures must have backup data that is readily available for review and audit.

6.5 Transfer of Analytical Test Procedures

Testing materials for compliance to specifications is critical in establishing the quality of the dietary supplement. The transfer of analytical procedures (TAP), also referred to as method transfer, is the documented process that qualifies a laboratory (the receiving unit) to use an analytical test procedure that originated in another laboratory (the transferring unit), thus ensuring that the receiving unit has the procedural knowledge and ability to perform the transferred analytical procedure as intended. *USP* general chapter *Transfer of Analytical Procedures ⟨1224⟩* summarizes the types of transfers that may occur and outlines the potential components of a transfer protocol, and should be consulted to qualify a laboratory (both internal and external to the manufacturer) to ensure it has the procedural knowledge and ability to perform the test procedure as intended.

6.6 Reduced Testing

6.6.1 GENERAL

Reduced testing or inspection provides a way of reducing the testing or inspection effort on received components, in-process material, and dietary supplements of high quality, in which all batches are expected to be of the similar quality.

Reduced testing for a particular specified parameter(s) should be based upon one or more of the following:

- Statistical analysis of an adequate quantity of historical test data;
- Statistical confidence in the capability of the manufacturing process as determined by suitable verification; and
- Ongoing monitoring of the process using recognized statistical process control (SPC) techniques.

Control procedures should be established to monitor the output of manufacturing processes that may cause variability for in-process material and dietary supplements, which may include, but are not limited to: clarity, completeness, or pH of solution; blend uniformity; friability; weight variation or content uniformity; and disintegration or dissolution time.

The following terms are useful when describing reduced testing:

- Lot-by-lot inspection means inspection of products submitted in a series of lots;
- Reduced sampling inspection means a sampling inspection procedure in which some lots in a series are accepted without full testing when the sampling results for a stated number of immediately preceding lots meet stated criteria;
- Inspection sampling frequency means probability that a lot is fully tested (e.g., every fifth lot);
- Disqualification means failure to qualify for reduced sampling inspection;
- Requalification means qualification for a resumption of reduced sampling inspection;
- Supplier qualification means assessment of the supplier's GMP competence so as to implement reduced sampling inspection;
- Product qualification means assessment of product (i.e., component, in-process material, or dietary supplement) quality to determine its suitability for reduced sampling inspection.

6.6.2 REDUCED TESTING REQUIREMENTS

Reduced sampling inspection may only be used when both the supplier's GMP quality systems and product (i.e., the component, in-process material, or dietary supplement) are qualified. See *1.7 Supplier Qualification* for guidance.

- Requirements for supplier qualification:
  - The supplier must have established, documented, and followed effective and applicable GMP quality systems for managing quality that involves the active participation of personnel;
  - An assessment of the supplier's GMP quality systems must be performed;
  - Ongoing assessment of the supplier's GMP quality systems should be performed on a specified frequency; and
  - The supplier must not have experienced changes in its GMP quality systems that adversely affect product quality.

- Requirements for product (i.e., component, in-process material or dietary supplement) qualification:
  - An assessment for product qualification should not be made prior to the assessment of the supplier's GMP quality systems;
  - The preceding three (3), at minimum, or more consecutive lots have been accepted, and results of resubmitted lots are not included.

The following are examples of typical reduced inspection and rotational testing that can be performed:

- Reduced testing, for example, a typical approach:

- Conduct lot-by-lot full inspection on the first 3 lots;
- If successful, conduct reduced sampling inspection on every fifth (5th) lot for a set period of time;
- If successful, reduce sampling inspection to every tenth (10th) lot, until there is a failure;
- Test a minimum of 1 lot every year; and
- If a failure is encountered, disqualify the supplier and its product, and conduct a root cause investigation and return to full testing of the next 3 lots.

- Rotational testing, for example, a typical approach:
  - Establish testing levels, e.g., I, II, III, specifying what tests on the product specification are to be conducted on a given lot in sequence (i.e., I, II, III), such that all test on the product specification are tested at least once on every 3 lots;
  - A subset of tests should be selected for identification, potency, limit of contaminants, and performance;
  - Tests for key potential contaminants are conducted for every lot; and
  - Some critical tests are conducted for every lot.

6.6.3 RECEIVED COMPONENTS, IN-PROCESS MATERIALS, AND DIETARY SUPPLEMENTS

On the basis of adequate supplier qualification, process validation, in-process controls, and statistical confidence, a reduced testing plan is an alternative to fully testing every batch of components received from a supplier provided that at least one identity (i.e., identification) test is conducted. Such identification tests must include sufficient specificity to determine the identity of the component.

Each batch of components received from a supplier that is liable to be contaminated with microorganisms, filth, insect infestation, allergens, aflatoxins, other natural toxins, pesticides, organic impurities (e.g., residual solvents), and/or inorganic impurities (e.g., foreign substances, or other extraneous substances that may be a source of contamination that is objectionable in view of its intended use) must be tested or examined against established specifications for such contamination. In such cases, reduced testing of examination must not apply until risk is mitigated by the supplier.

6.6.4 IN-PROCESS MATERIALS AND DIETARY SUPPLEMENTS

On the basis of process validation, in-process controls, and statistical confidence, a reduced testing plan is an alternative to fully testing every batch of in-process material and dietary supplements provided that at least one representative measure (i.e., rotational testing) is performed.

6.7 Out-Of-Specification (OOS) Investigations

Written procedures must be established and followed for investigating critical deviations or the failure of a batch of material to meet specifications (i.e., out-of-specification investigations), and corrective action plans must be established for use when an established specification is not met. The investigation should extend to other batches that may have been associated with the specific failure or deviation. The procedure should require analysis of the data, assessment of whether a significant problem exists, allocation of the tasks for corrective actions, and conclusions. Any resampling and/or retesting after OOS test results should be performed according to a documented procedure. Regulatory guidance for investigating OOS test results should be consulted.

6.8 Stability Testing

A documented on-going testing program must be designed to monitor the stability characteristics of dietary supplements, and the results must be used to establish appropriate storage conditions and shelf life (expiry) dates for the dietary supplements. Test procedures used in stability testing must be validated. Stability samples should be stored in container-closure systems that simulate the packaging proposed to distribute the finished dietary supplement in the marketplace. Stability studies should include testing of those attributes of the dietary supplement that are susceptible to change during storage and that influence the quality of the dietary supplement.

Ideally the first three (3), but at minimum one (1), production batch(s) should be placed on the stability monitoring program to establish the product shelf life (expiry) date. Ideally, thereafter, at least one (1) batch per year of manufactured dietary supplement (unless none is produced that year) should be added to the stability monitoring program.

As appropriate, the stability storage conditions for temperature and relative humidity (RH) should be as follows:

- Long term = 25 ± 2° and 60 ± 5% RH;
- Intermediate = 30 ± 2° and 65 ± 5% RH;
- Accelerated = 40 ± 2° and 75 ± 5% RH.

Long term studies can also be performed under the labeled storage conditions, e.g., at room temperature (ambient conditions), or in a cool, dry place (8°–15° and NMT 40% RH). Alternative storage conditions should be considered for products marketed outside the United States in different climatic zones.

The frequency of testing should be sufficient to establish the stability profile of the dietary supplement. The following testing frequencies are recommended:

- Long term = 0, 3, 6, 9, 12, 18, and 24 months;
- Intermediate = 0, 3, 6, 9, and 12 months;
- Accelerated = 0, 1, 2, 3, and 6 months.

For long term studies, frequency of testing should be sufficient to establish the stability profile of the dietary supplement.

Accelerated stability studies are designed to increase the rate of chemical degradation or physical change and are intended to evaluate the effect of short-term excursions outside the labeled storage conditions such as might occur during shipping. Although accelerated stability

studies may not adequately reflect the stability of the product under labeled (e.g., long term) conditions, results from accelerated stability can be used to estimate a preliminary shelf life (expiry) date for a dietary supplement that should eventually be supported with data from long term stability studies.

Preliminary shelf life (expiry) dates can be based on pilot scale batches if the pilot batch is at least one-tenth (1/10th) the size of the commercial batch size and the pilot batch employs a manufacturing process that simulates the process to be used on a commercial manufacturing scale. Bench scale batches should not be used for stability studies.

In certain cases, dietary supplements being closely related in composition may be grouped together using one representative dietary supplement formulation with which to obtain stability data to support the shelf life (expiry) date of all dietary supplement formulations within that group. Under such circumstances, sufficient scientific justification should be provided as to support grouping of the dietary supplements for stability purposes.

The design of the stability studies may also bracket dietary supplements such that only dietary supplements on the extremes of certain factors, e.g., strength, package size, are tested. This design assumes that the stability of any intermediate level is represented by the stability of the extremes tested.

Stability studies should be performed for dietary supplements packaged in different container–closure systems [e.g., high density polyethylene (HDPE) bottles, polyethylene terephthalate (PET) bottles, blister packs]. In certain cases, stability data using one type of container–closure system may be used to support stability of the product in a different type of container–closure system (e.g., HDPE versus PET bottles) with supporting scientific justification regarding the moisture, vapor, and light protection characteristics of the two types of container–closure systems.

Long term and accelerated (and intermediate) stability studies should be undertaken according to a prescribed stability protocol. The resultant data must be properly evaluated. The degree of variability of stability data between or within individual batches affects the confidence in the data. The data may show little degradation and little variability such that it is apparent from looking at the data that the product will meet specifications throughout the proposed shelf-life (expiry) date. When the data on a quantitative attribute changes with time and shows significant degradation or significant variability, it is necessary to use formal statistical analysis to determine the shelf life (expiry) date for the dietary supplement. A stability report should be prepared for the dietary supplement stating the proposed storage conditions and shelf life (expiry) date of the dietary supplement(s), along with the stability data and its evaluation.

6.9 Laboratory Testing Records

Laboratory control records should include complete data derived from all tests conducted to ensure compliance with established specifications and standards, including examinations and assays, as follows:

- A description of samples received for testing, including material name or source, batch number or other distinctive code, date sample was taken, and, where appropriate, the quantity and date the sample was received for testing;
- A statement or reference to each test procedure used;
- A statement of the weight or measure of sample used for each test as described by the test procedure;
- Data on or cross-reference to the preparation and testing of reference standards, reagents, and standard solutions;
- A complete record of all raw data generated during each test, in addition to graphs, charts, and spectra from laboratory instrumentation, properly identified to show the specific material and batch tested;
- A record of all calculations performed in connection with the test, including, for example, units of measure, conversion factors, and equivalency factors;
- A statement of the test results and how they compare with established acceptance criteria;
- The signature of the person who performed each test and the date(s) the tests were performed; and
- The date and signature of a second person showing that the original records have been reviewed for accuracy, completeness, and compliance with established procedures.

A certificate of analysis (CoA) should be issued for each batch of dietary supplements. The certificate of analysis should list the name and item code of the dietary supplement, the batch number, the release date, and the expiry date. The CoA should list each test performed, the specific identity of the test procedure, the acceptance limits or criteria, and the results with numerical units, as appropriate. The CoA should be dated and signed by authorized quality unit personnel. For CoA issued for external use, the CoA should list the name, address, and telephone number of the manufacturer.

6.10 Quality Control Unit Responsibilities for Laboratory Operations and Controls

For laboratory operations, quality control unit personnel must:

- Review and approve all laboratory control processes associated with the production and process control system;
- Ensure that all tests and examinations required to determine compliance to specifications are conducted; and
- Review and approve the results of all tests and examinations required to determine compliance to specifications.

6.11 Laboratory Operations and Controls Documentation

The following documentation must be made and kept for fulfilling the requirements of the laboratory controls system (quality system 6).

6.11.1 WRITTEN PROCEDURES

Written procedure for laboratory operations must be established and followed for:

- The tests and examinations conducted to determine whether specifications are met;

- Establishing, reviewing, and approving material specifications;
- Preparation, review, and approval of written test procedures;
- Validating and verifying test procedures for their intended use;
- Selection, preparation, and handling of reagents and reference standards;
- Establishing, reviewing, and approving sampling plans, including reduced sampling inspections;
- Sampling, testing, approval, and rejection of materials, and recording and storage of laboratory data;
- Investigating critical deviations or out-of-specification test results; and
- Establishment and implementation of a stability testing program.

6.11.2 RECORDS

Records must be made and kept for:

- Documentation that established laboratory test and examination procedures are followed;
- The person who conducts the testing and examination must document, at the time of performance, that established laboratory methodology is followed;
- Documentation for laboratory tests and examinations must include the data and results of the testing and examination;
- Any modification to an established test procedure;
- Out-of-specification (OOS) investigations and corresponding corrective actions;
- Test procedure method validation or verification protocols and reports, supporting test procedure suitability for use;
- The periodic calibration of laboratory instruments and controls;
- Stability protocols and stability data and reports, supporting a product's shelf life (expiry) date.

GLOSSARY

Acceptance criteria: Predetermined limits (e.g., number, numerical ranges, or other suitable measures) for acceptance of examination or test results.

Adequate: Item/area/system/knowledge that meets basic minimum requirements that are needed to accomplish intended purpose.

Adulteration: A food shall be deemed to be adulterated if it contains any poisonous or deleterious substance as specified in §402(a)(1)–(2) of the FFDCA: or if it consists of any filthy, putrid, or decomposed substance, or if it is otherwise unfit for food as specified in §402(a)(3) of the FFDCA; or if it has been prepared, packed, or held under insanitary conditions as specified in §402(a)(4) of the FFDCA; or if its container is composed of any poisonous or deleterious substance which may render the contents injurious to health as specified in §402(a)(6) of the FFDCA; or if it has been intentionally subjected to radiation as specified in §402(a)(7) of the FFDCA; or if the contents have been altered, or if damage and or inferiority has been concealed as specified in §402(b)(1)–(4); or if it contains a color additive which is unsafe as specified in §402(c); or if it is a dietary supplement or contains a dietary ingredient that presents a significant or unreasonable risk of illness or injury as specified in §402(f)(1); or if it is a dietary supplement that has been prepared, packed, or held under conditions that do not meet current good manufacturing practice regulations as specified in §402(g)(1); or if it has not been transported in compliance with regulations as specified in §402(i).

Adverse event: Any undesirable experience associated with the use of a dietary supplement in a person.

Adverse event report: A direct communication from an identifiable first-hand reporter of an adverse event that includes at least the following information: an identifiable reporter, an identifiable person(s) who experienced the adverse event(s), an identifiable dietary supplement, and one or more adverse events.

Allergen cross-contact: The unintentional incorporation of a food allergen into a dietary supplement.

Allergen: A major food allergen as defined in §201(qq) of the FFDCA, means any of the following: (1) milk, egg, fish (e.g., bass, flounder, or cod), Crustacean shellfish (e.g., crab, lobster, or shrimp), tree nuts (e.g., almonds, pecans, or walnuts), wheat, peanuts, and soybeans; (2) a food ingredient that contains protein derived from a food specified in (1), except (A) any highly refined oil derived from a food specified in (1) and any ingredient derived from such highly refined oil, and (B) a food ingredient that is exempt under paragraphs (6) and (7) of §403(w) of the FFDCA.

Article: Includes substances (such as components, in-process material, dietary ingredients), products (such as dietary supplements), and materials (such as packaging containers and closures, and labels).

Audit: A planned, systematic, objective, independent, and documented examination (through observation, investigation, records review, discussions with employees of the audited firm, and, as appropriate, sampling and laboratory analysis) to assess whether agreed-upon requirements are being met.

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

Batch (or lot) number: 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.

Calibration: The demonstration that a particular instrument or device produces results within specified limits by comparison with those produced by a reference or traceable standard over an appropriate range of measurements.

Can: Used to indicate a possibility or a capability.

Certificate of analysis (CoA): A document relating specifically to the results of testing a representative sample drawn from the batch of material. The CoA should list each test performed in accordance with compendial or manufacturer requirements, including reference to the test procedure, the acceptance limits, and the results obtained.

Code of Federal Regulations: The *Code of Federal Regulations* (CFR) annual edition is the codification of the general and permanent rules and regulations published in the Federal Register by the executive departments and agencies of the federal government of the United States. It is structured into 50 subject matter titles; title 1 applies to general provisions, and title 21 applies to food and drugs. Titles are broken down into parts, subparts, sections, and paragraphs. For example, 21 CFR §11.10(k)(2) would be read as title 21, part 11 (subpart B, not specified here), section 10, paragraph (k)(2). The CFR annual edition is published by the Office of the Federal Register, National Archives and Records Administration and the Government Publishing Office. In addition to this annual edition, the CFR is published in an unofficial format online in electronic format (eCFR), which is updated daily.

Component: 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.

Composition: The specified mix of product and product-related substances, i.e., specified mix of food ingredients or excipients and dietary ingredients in a dietary supplement.

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

Contamination: The undesired introduction of a chemical or microbiological nature, or of foreign matter, into or onto a component, in-process material, or dietary supplement during production, sampling, packaging, repackaging, storage, or transport.

Contract manufacturer: A manufacturer performing some aspect of manufacturing on behalf of the original manufacturer.

Corrective action: An action that is developed and implemented to ensure that any identified root cause of a nonconformity does not recur.

Critical: Describes a manufacturing process step, process condition, test requirement, or other relevant parameter or item that must be controlled within predetermined criteria to ensure the dietary supplement meets its specification.

Design qualification (DQ): DQ is the documented collection of activities that defined the functional and operational specifications and intended purpose of the equipment or instrument. DQ states what the user wants the equipment or instrument to do and shows that the selected equipment or instrument is suitable.

Defect action level: A level of a non-hazardous, naturally occurring, unavoidable defect at which FDA may regard a food product “unadulterated” and subject to enforcement action under §402(a)(3) of the FFDCA.

Deviation: Departure from an approved instruction or procedure, or from an established standard (i.e., a failure, or an out of specification result). Deviations can be planned, or unplanned (i.e., a nonconformity).

Dietary ingredient: An ingredient intended for use or used in a dietary supplement that is: a vitamin; a mineral; an herb or other botanical; an amino acid; a dietary substance for use by man to supplement the diet by increasing the total dietary intake, or a concentrate, metabolite, constituent, extract; or a combination of the aforementioned ingredients.

Dietary supplement: A product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following dietary ingredients: a vitamin; a mineral; an herb or other botanical; an amino acid; a dietary substance for use by man to supplement the diet by increasing the total daily intake; or a concentrate, metabolite, constituent, extract or combination of the aforementioned ingredients; that is intended for ingestion in a tablet, capsule, powder, softgel, gelcap, or liquid form; that is not represented for use as a conventional food or as a sole item of a meal or the diet; and is labeled as a dietary supplement; and does include an article approved as a new drug, certified antibiotic, or licensed biologic, and was prior to such approval, certification, or license, marketed as a dietary supplement or food unless the Secretary of Health and Human Services has issued a regulation finding that the article, when used as or in a dietary supplement under the conditions of use and dosages set forth in the labeling for such dietary supplement is unlawful.

Disposition decision: A decision to approve or reject material, quality control, and manufacturing related processes or documents, based on a scientifically valid reason. Disposition decisions can be made regarding release of components, in-process materials, dietary supplements, packaging materials, labels, returned dietary supplements, based on a determination of whether or not established specifications are met; or regarding reprocessing treatments and in-process adjustments, master manufacturing records and batch production records, repackaging or relabeling, calibrations of an instrument or control, modification or deviations from standard procedures, and whether or not a deviation or unanticipated occurrence during the production and in-process control system could lead to adulteration of a dietary supplement.

Documentation: Written material related to the requirements of the quality system, including paper and electronic records, that consist of raw data, reports, protocols, and procedures related to manufacturing controls and laboratory testing. Official documents are records that support procedures, products, or the manufacturer’s quality systems (e.g., standard operating procedures, master batch records, material specifications, standard test procedures, protocols, reports). Source documents are records that contain original data or information (e.g., forms, notebooks, logbooks, instrument printouts).

Equipment: Devices used to manufacture, package, or hold dietary supplements, or to maintain or clean the physical plant and devices.

Facility: A place, amenity, utility, or piece of equipment provided for a particular purpose.

Federal Food, Drug, and Cosmetic Act: Federal Food, Drug and Cosmetic Act (FFDCA or FD&C Act) [United States Code (USC) title 21, chapter 9] is the official compilation and codification of the federal statutes of the US that gives authority to the Food and Drug Administration (FDA) oversee the safety of food, drugs, medical devices and cosmetics in the US.

Ingredient: 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.

In-process control (or process control): Checks performed during production in order to monitor and, if appropriate, to adjust the process and/or to ensure the dietary supplement conforms to its specification.

In-process material: 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.

In-process test: A test that may be performed during the manufacture of the dietary supplement, rather than as part of the formal battery of tests that are conducted prior to release.

Instrument (or instrumentation): A sophisticated measuring device or tool used for analytical or scientific work.

Installation qualification (IQ): The documented collection of activities necessary to establish that an equipment or instrument is delivered as designed and specified, is properly installed in the selected environment, and that the environment is suitable for the instrument.

Label: A display of written, printed, or graphic matter upon the immediate container of a dietary supplement.

Labeling: All labels and other written, printed, or graphic matter upon any dietary supplement or any of its containers, or wrappers, or accompanying such dietary supplement at any time while the dietary supplement is held for sale after shipment or delivery for shipment in interstate commerce. The term “accompanying” is interpreted liberally to mean more than physical association with the dietary supplement. It extends to posters, tags, pamphlets, circulars, booklets, brochures, fillers, etc.

Lot: A batch, or a specific identified portion of a batch, that is intended to be uniform and that is intended to meet specifications for identity, purity, strength, and composition.

Manufacture: All operations of receipt of components, production, packaging, labeling, quality control testing, release, storage, and distribution of dietary supplements and related controls.

Material: A general term used to denote components, in-process materials, dietary supplements, and packaging and labeling material.

May: Used to indicate a permission.

Microorganism: Any yeasts, molds, bacteria, viruses, or other microscopic organisms having public health or sanitary concern. This includes undesirable species that may have public health significance; that may cause a component or dietary supplement to decompose; that indicate that a component or dietary supplement is contaminated with filth; or that otherwise may cause a component a dietary supplement to be adulterated.

Must: Used to state a requirement.

Nonconformity: An event that occurs when a specified requirement is not met or results from an undesirable situation or defect. This covers departure from a procedure, standard or requirement, or the absence of dependability. This typically arises from the inability to meet documented procedures, expectations or specifications.

Operational qualification (OQ): OQ is the documented collection of activities necessary to demonstrate that an equipment or instrument will function according to its operational specification testing in the selected environment. OQ demonstrates fitness for the selected use and demonstrates user requirement specifications.

Packaging material: Container and/or closure for components, in-process material and dietary supplements.

Performance qualification (PQ): PQ is the documented collection of activities necessary to demonstrate that an equipment or instrument consistently performs according to the specifications defined by the user, and is appropriate for the intended use. PQ verifies the fitness for purpose of the equipment or instrument under actual conditions of use.

Pest: Any objectionable insect or other animal including, but not limited to, birds, rodents, flies, mites, and larvae.

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

Preventive action: An action taken to eliminate the cause of potential nonconformities or other undesirable situations in order to prevent occurrence, and continuously improve an existing system or process.

Preventive controls qualified individual (PCQI): A qualified individual who has successfully completed training in the development and application of risk-based preventive controls at least equivalent to that received under a standardized curriculum recognized as adequate by FDA or is otherwise qualified through job experience to develop and apply a food safety system.

Procedure: A documented description of the operations to be performed, the precautions to be taken, and measures to be applied directly or indirectly related to the manufacture of a dietary supplement.

Process evaluation: A set of tests performed on a process intended to evaluate its capacity to consistently produce the results that it is intended for.

Product complaint: 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 manufacturing practice.

Purity: The identity and amount of a substance that is the intended substance, typically expressed in units of percentage, and determined using tests for assay or content.

Qualification: Action of proving and documenting that equipment or ancillary systems are properly, work correctly, and actually lead to the expected results. Qualification is part of validation, but the individual qualification steps alone do not constitute process validation.

Quality: Means that the components, in-process materials, packaging materials, labeling, and dietary supplements meet established specifications for identity, purity, strength and composition, and limits on contaminants, and that the dietary supplement has been manufactured, packaged, labeled, and held under conditions to prevent adulteration.

Quality assurance: The sum total of the organized arrangements made with the goal of ensuring that all dietary supplements are of the quality required for their intended use and that quality systems are maintained.

Quality assurance personnel (or unit): Any person, persons or group, within or outside of the firm who is designated by the firm to be responsible for the duties relating to quality assurance.

Quality control: A planned and systematic operation or procedure necessary to ensure the quality of the dietary supplement, by checking or testing that specifications are met.

Quality control personnel (or unit): Any person, persons or group, within or outside of the firm, who is designated by the firm to be responsible for the duties relating to quality control operations.

Quality unit (or personnel): An organizational unit independent of production, which fulfills both quality assurance and quality control responsibilities, which can be in the form of separate quality assurance and quality control units or a single individual or group, depending upon the size and structure of the organization.

Quarantine: The status of materials isolated physically or by other effective means pending a decision on their subsequent disposition decision.

Records: Records are documents stating results achieved or providing evidence of activities performed, e.g., training records, executed batch production records, executed batch packaging records, validation reports, laboratory test results forms, laboratory notebooks, equipment logbooks, memos, and emails.

Reduced testing (or **sampling):** A reduced level of testing (or sampling) for a particular specified parameter(s) based upon one or more of the following: statistical analysis of an adequate quantity of historical test data; statistical confidence in the capability of the manufacturing process as determined by suitable verification; or ongoing monitoring of the process using recognized statistical process control (SPC) techniques.

Reference standard, primary: A substance that has been shown by an extensive set of analytical tests to be authentic material that should be of high purity. This standard is obtained from an officially recognized source, i.e., USP RS.

Reference standard, secondary: A substance of established quality and purity, as shown by comparison to a primary reference standard, used as a reference standard for routine laboratory analysis.

Remedial (short term) action: Action taken to provide temporary control over a situation or condition until permanent corrective actions are implemented (e.g., issuance of a temporary procedure, segregation of material).

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

Reprocessing: Introducing clean and uncontaminated components or dietary supplements, back into the manufacturing process and repeating a step or other appropriate physical manipulation step (e.g., milling, packaging) that are part of the established manufacturing process. Continuation of a manufacturing process step after an in-process control test has shown that the step is incomplete is considered to be part of the normal manufacturing process and not reprocessing.

Responsible party: The person who submits the registration under section 415(a) of the FD&C Act (21 USC 350(d)) for a food facility that is required to register under section 415(a), at which such article of food is manufactured, processed, packed, or held. Persons who are required to submit a facility registration under section 415 of the FD&C Act are the owner, operator, or agent in charge of a domestic or foreign facility engaged in manufacturing, processing, packing, or holding food for consumption in the United States. “Person” is defined in section 201(e) of the FD&C Act (21 USC 321(e)) as including individuals, partnerships, corporations, and associations.

Reworking: Subjecting in-process material or dietary supplements that do not conform to standards or specifications and that have been removed from processing for reasons other than unsanitary conditions, to one or more processing steps that are different from the established manufacturing process to obtain acceptable quality in-process material or dietary supplement.

Reserve sample: A representative sample of an article that is held for a designated period of time.

Risk: The combination of the probability of occurrence of harm and the severity of that harm.

Risk assessment: A systematic process of organizing information to support a risk decision to be made within a risk management process. It consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards.

Risk control: Actions implementing risk management decisions to reduce risk and/or accept risks in order to reduce risk to an acceptable level.

Risk management (quality): A systematic process for the assessment, control, communication, and review of risks to the quality of the dietary supplement throughout the dietary supplement’s shelf life. Risk management tools that might be used in quality risk management include facilitation methods (e.g., flowcharts, check sheets, process mapping, cause and effect diagrams); failure mode effects analysis (FMEA); failure mode, effects, and criticality analysis (FMECA); fault tree analysis (FTA); hazard analysis and critical control points (HACCP); and supporting statistical tools (e.g., control charts, histograms, pareto charts, process capability analysis, design of experiments).

Root cause: Any cause that is acted upon by a solution such that the problem does not recur.

Sanitize: To adequately treat cleaned equipment, containers, utensils, or 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.

Serious adverse event: An event that results in death, a life-threatening experience, inpatient hospitalization, a persistent or significant disability or incapacity, or a congenital anomaly or birth defect; or requires based on a reasonable medical judgment, a medical or surgical intervention to prevent an outcome previously described.

Serious adverse event report: A report that must be submitted to the FDA using the MedWatch form when a manufacturer, packer, or distributor of a dietary supplement receives any report of a serious adverse event associated with the use of the dietary supplement in the United States. (See §761(a)(3) and (b)(1) of the FD&C Act [21 USC §379aa–1(a)(3) and (b)(1)]).

Shelf-life (use by or **expiry) date:** The date before which the dietary supplement is ensured to meet applicable specifications of identity, strength, quality, and purity, when stored under labeled conditions.

Should: Used to indicate a recommendation.

Signature (signed): The record of the individual who performed a particular action or review. This record can be initials, full handwritten signature, or authenticated and secure electronic signature.

Specification: A list of tests, references to test procedures, and appropriate acceptance criteria for the tests described. It establishes the set of criteria to which a material should conform to be considered acceptable for its intended use. “Conformance to specifications” means that the

component, in-process material, and/or dietary supplement, when tested according to the listed test procedures, will meet the listed acceptance criteria. Specifications are critical quality standards that are proposed, justified and approved by the manufacturer. Material specifications include test specifications for identity, purity, strength, limits on contaminants, and/or performance that define a standard of quality for the material.

Strength: The concentration or amount of a dietary ingredient per unit serving of a dietary supplement. Strength only applies to a dietary supplement.

Utensil: A simple tool or device serving a useful purpose.

Utility system (utility): A useful system and source of material such as water, steam, gases, compressed air, heating, ventilation, and air conditioning (HVAC).

Validation: A documented program that provides a high degree of assurance that a specific process, method, or system will consistently produce a result meeting predetermined acceptance criteria.

Validation protocol: A written plan stating how validation will be conducted and defining acceptance criteria. For example, the protocol for a manufacturing process identifies manufacturing equipment, critical process parameters/operating ranges, product characteristics, sampling, test data to be collected, number of validation runs, and acceptable test results.

Water activity (a_w): 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.

Yield, actual: The quantity of material or percentage of theoretical yield that is actually produced at any appropriate step of production, or packaging and labeling of a particular dietary supplement.

Yield, expected: The quantity of material or the percentage of theoretical yield anticipated at any appropriate phase of production, or packaging and labeling, based on previous laboratory, pilot scale, or manufacturing data.

Yield, theoretical: The quantity of material that would be produced at any appropriate step of manufacture or packaging and labeling of a particular dietary supplement, based on the quantity of components, packaging labeling to be used, in the absence of any loss or error in actual production.

Reference Table: Sections of 21 CFR Used in this Chapter

⟨2750⟩	21 CFR
1. QUALITY MANAGEMENT	
1.2 Organization and Personnel	§§111.105(a), 111.12(a)–(c), 111.113(a)–(c), 111.14(b)(2),111.10(a)(1)&(2), and 111.10(b)(1)–(9)
1.3 Documentation and Records	§§111.605(a)–(c) and 111.610(a)–(b)
1.5 Deviations and Material Reviews	§§111.103, 111.140(b)[(1)–(2)(i)–(ii)&(3)], 111.87, 111.113(a)–(b), and 111.77(a)
1.7 Supplier Qualification	§§117.405(a)–(c), 117.126(b), 117.410(a)(1)–(2), (b)(1)–(4)&(d), 117.420(a), 117.430(a), 117.425, and 111.105(b)
1.9 Complaints, Serious Adverse Event Reporting, and Recalls	§§111.553, 111.570(b)(1)–(2), 111.560(a)(1)–(2)(b)&(c), and 111.135
1.12 Quality Management Documentation	§§111.14(b)(1), 111.103, 140(b)(1)–(2), 111.553, and 111.570(b)(1)–(2)
2. PHYSICAL PLANT AND EQUIPMENT	
2.1 Grounds Maintenance	§111.15(a)(1)–(5)
2.2 Physical Plant Design	§111.20
2.3 Physical Plant Sanitation and Facilities	§§111.15 and 117.20(b)(2)
2.4 Equipment, Instruments, and Utensils	§§111.27(a)–(d), 111.30(a)–(d), 111.117(a)–(d), and 111.605(c)
2.5 Physical Plant and Equipment Documentation	§§111.16, 111.23, 111.25(a)–(c), and 111.35(b)(1)–(6)
3. MATERIALS MANAGEMENT AND CONTROLS	
3.1 Establishing Material and In-Process Production Specifications	§111.70(a)–(g)

⟨2750⟩	21 CFR
3.2 Determining Compliance with Specifications	§111.73, 111.105(d)–(h), 111.75(a)–(i), 111.77(a)–(c), 111.123(b)(1)–(4), and 111.90
3.3 Receiving and Release of Materials	§§111.155, 111.160, and 111.165 (a)–(e)
3.4 Representative Samples and Reserve Samples	§§111.80 and 111.83
3.5 Holding, Distribution, and Transportation	§§111.453, 111.455, 111.460 (a)–(b), 117.80(b)(8), 111.465(a)–(b), 111.170, 111.370, 111.510, 111.515, 111.520, 111.525, 111.470, 1.908, 1.906, 1.912
3.6 Quality Unit Responsibilities for Materials Management Operations	§§111.120 and 111.130(a)–(d)
3.7 Materials Management Operations and Controls Documentation	§§111.180(b)(1)–(3), 111.475(b), 111.503, 111.535(b)(1), 111.95(b)(1)–(4), and 111.140(b)(2)
4. PRODUCTION OPERATIONS AND CONTROLS	
4.1 Master Manufacturing Records	§§111.205(b) and 111.210(a)–(h)
4.2 Executed Batch Production Records	§§111.255(a)–(c) and 111.260(a)–(n)
4.3 Manufacturing Operations Production and Process Controls	§§111.355, 111.360, and 111.365
4.4 Quality Unit Responsibilities for Production	§111.123
4.5 Disposition Decision for Production	§111.123(b)(1)–(4)
5. PACKAGING AND LABELING OPERATIONS AND CONTROLS	
5.2 Packaging Materials	§111.410(a)
5.4 Labeling Issuance and Control	§111.410(b)
5.5 Packaging and Labeling Operations	§§111.415(a)–(h), 111.410, 111.83(b)(3)&(4), and 111.425
5.6 Repackaging and Relabeling	§111.420(a)–(c)
5.7 Quality Unit Responsibilities for Packaging and Labeling Operations	§111.127(a)–(h)
6. LABORATORY OPERATIONS AND CONTROLS	
6.1 General	§§111.310(a)–(c) and 111.315
6.10 Quality Control Unit Responsibilities for Laboratory Operations and Controls	§111.110(a)–(c)
6.11 Laboratory Operations and Controls Documentation	§§111.325(b)(1), 111.325(b)(1)–(2), and 111.325(b)(2)(i)–(ii)▲ (USP 1-Aug-2021)

Auxiliary Information - Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
<2750> MANUFACTURING PRACTICES FOR DIETARY SUPPLEMENTS	Natalia Davydova Scientific Liaison	NBDS2020 Non-botanical Dietary Supplements

Most Recently Appeared In:
Pharmacopeial Forum: Volume No. 46(2)
Current DocID: GUID-B1EB10D3-6473-4AC9-99B7-4AD444683A01_2_en-US
DOI: https://doi.org/10.31003/USPNF_M99987_02_01
DOI ref: 0pf8r