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**Add the following:**

# **^⟨2740⟩ MANUFACTURING PRACTICES FOR DIETARY INGREDIENTS**

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### **1. GENERAL PROVISIONS**

This general information chapter provides recommended minimum good manufacturing practices for the methods to be used in and the facilities and manufacturing controls to be used for the manufacture, holding, packaging, labeling, and distribution of dietary ingredients. These principles are set forth to assist manufacturers as well as auditors in establishing whether the facilities and controls used for the manufacture of dietary ingredients are adequate and whether the dietary ingredients possess the identity, strength, and meet the quality and purity characteristics that they purport to possess.

The requirements pertaining to dietary ingredients apply to determining whether or not a dietary ingredient is adulterated within the meaning of §402(a)(3) of the US Federal Food, Drug, and Cosmetic Act (FD&C Act) in that the dietary ingredient has been manufactured under such conditions that is unfit for food; or §402(a)(4) of the FD&C Act in that the food has been prepared, packed, or held under insanitary conditions whereby it may have become contaminated with filth, or whereby it may have been rendered injurious to health; and in violation of §361 of the Public Health Service Act (42 USC §264). The operation of a facility that manufactures, processes, packs, or holds food for sale in the United States if the owner, operator, or agent in charge of such facility is required to comply with, and is not in compliance with, §418 of the FD&C Act or Subpart C, D, E, or F of this part is a prohibited act under §301(UU) of the FD&C Act.

A production and in-process control system must be designed and implemented to cover all stages of manufacturing, packaging, labeling, holding, and distribution of the dietary ingredient and that is designed to ensure quality as specified in the batch production, packaging control record, and dietary ingredient specification.

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

1. *Quality management system*—This system assures overall compliance with current good manufacturing practices (cGMPs) and internal procedures and specifications. This system includes the quality control (QC) unit and all of its review and approval duties (e.g., change control, deviations and material reviews, batch release, product quality review, validation protocols, and reports, etc.). It also includes Hazard Analysis and Risk-Based Preventive Controls (HARPC) or the Hazard Analysis Critical Control Points (HACCP) which details the food safety plan (FSP), food allergen controls, sanitation controls, supply-chain program, and HARPC implementation records. The quality management system must define the quality unit's 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 that provide an appropriate physical environment and resources used in the manufacture of dietary ingredients. It includes buildings and facilities along with maintenance, equipment qualifications, calibration and preventative maintenance, computerized systems, and utilities that are not intended to be incorporated into the product such as water systems.
3. *Materials management system*—This system includes measures and activities to control dietary ingredients including specifications and determining compliance with specifications. It also includes the procedures and process for receiving and release of materials and collecting representative and reserve samples along with storage, distribution controls, and records. The materials management system also includes electronic systems that are used to quarantine and control the movement of physical inventory to ensure that only approved and released materials are allocated to a production order.
4. *Production operations and controls system*—This system includes measures and activities to control the manufacture of dietary ingredients, including batch and continuous production and control records, production and process controls, and operation and control documentation. This system also includes an evaluation of automatic electronic weighing and control systems that are designed to minimize the potential for errors in production.
5. *Packaging and labeling operations and controls system*—This system includes measures and activities that control the packaging and labeling of dietary ingredients. It includes written procedures, label examination and usage, on-site label printing, 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.

## 2. QUALITY MANAGEMENT

### 2.1 General Principles

Quality unit operations must be implemented in manufacturing, packaging, labeling, laboratory, and holding operations for producing the dietary ingredients to ensure the quality of the dietary ingredient and that the dietary ingredient is packaged and labeled as specified in the master manufacturing and packaging control record.

Quality should be the responsibility of all persons involved in manufacturing, testing, packaging, labeling, and holding dietary ingredients. 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 ingredient 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 that fulfills both quality assurance (QA) and 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, and then signed and dated.

### 2.2 Organization and Personnel

#### 2.2.1 GENERAL

The owner, operator, or facility in charge and the management of the establishment must take reasonable measures and precautions to ensure all individuals who manufacture, process, pack, or hold dietary ingredients are qualified to perform their assigned duties.

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. 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.

#### 2.2.2 RESPONSIBILITIES OF THE QUALITY UNIT

A quality unit must be established that is involved in all quality-related matters and that must review and approve all appropriate quality-related documents. Quality unit personnel must ensure that manufacturing, packaging, labeling, and holding operations ensure the quality of the dietary ingredient and that the dietary ingredient is packaged and labeled as specified in the master production and control record.

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

- Establishing the HARPC and FSP
- Approving or rejecting (i.e., making a disposition decision for) the release of all dietary ingredients for distribution or of in-process materials for use outside the control of the manufacturer
- Establishing a system to approve or reject the release of raw materials, other ingredients, in-process materials, packaging materials, labeling materials, and the finished dietary ingredient
- Reviewing and approving or rejecting the release of products manufactured, packaged, labeled, or held under contract by another company
- Reviewing and approving all specifications and master production, packaging, and labeling records
- Reviewing and approving all procedures affecting the quality of in-process materials and dietary ingredients
- 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 deviations are investigated and resolved
- Ensuring that corrective and preventive actions as a result of investigations (deviations or complaints) and internal audits are implemented in a timely manner
- Ensuring that internal audits (self-inspections) are performed
- Establishing a supply chain control system to evaluate and approve suppliers of raw materials, other ingredients, packaging materials and labeling, and 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 ingredients
- 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 retest or expiry date and labeled storage conditions of dietary ingredients
- Performing product quality reviews and trend analysis, as needed

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

The quality unit personnel must be identified and qualified to perform QA and/or QC operations and have responsibilities related to performing quality unit operations distinct and separate from responsibilities that person otherwise has when not performing such operations.

The designated QC personnel who conducts a material review and makes the disposition decision must, at the time of performance, document any material review and disposition decisions.

### 2.2.3 RESPONSIBILITIES OF THE PREVENTIVE CONTROLS-QUALIFIED INDIVIDUAL AND QUALIFIED AUDITOR

One or more preventive controls-qualified individuals must do or oversee the following:

- Preparing the HARPC and FSP
- Validating the preventive controls
- Writing justification for validation to be performed in a time frame that exceeds the first 90 calendar days of production of the applicable dietary ingredient
- Determining that validation is not required with written justification
- Reviewing records
- Writing justification for review of records of monitoring and corrective actions within a time frame that exceeds 7 working days
- Re-analyzing the FSP
- Determining that re-analysis can be completed, and additional preventive controls validated as appropriate to the nature of the preventive control and its role in the facility's food safety system, in a time frame that exceeds the first 90 calendar days of production of the applicable dietary ingredient

To be a preventive controls-qualified individual, the individual must have 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 the FDA or be otherwise qualified through job experience to develop and apply a food safety system. Job experience may qualify an individual to perform these functions if that experience has provided knowledge at least equivalent to that provided through the standardized curriculum. The preventative controls-qualified individual may be, but is not required to be, an employee of the facility.

A qualified auditor must conduct an on-site audit. To be a qualified auditor, a qualified individual must have technical expertise obtained through education, training, or experience (or a combination thereof) necessary to perform the auditing function.

All applicable training in the development and application of risk-based preventive controls must be documented in records, including the date of the training, the type of training, and the person(s) trained.

### 2.2.4 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 ingredients 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 HVAC, dust collection, and other systems are appropriately designed to minimize the potential for cross-contamination
- Ensuring that physical and spatial separation are used in combination to minimize the potential for cross-contamination and to prevent mix-ups, when appropriate
- Ensuring that the premises and equipment are maintained and records are kept
- Ensuring that manufacturing process validation protocols and reports are reviewed and approved
- Evaluating proposed changes in product, process, or equipment
- Ensuring that new and any modified facilities and equipment are qualified through an appropriate documented change control system

### 2.2.5 PERSONNEL QUALIFICATIONS

Each person engaged in the manufacture of dietary ingredients (including temporary and seasonal personnel) or in the supervision thereof must be a qualified individual having the proper education, training, and experience (or any combination thereof) needed to perform the assigned functions.

Responsibility for ensuring compliance by individuals with the requirements of this general information chapter must be clearly assigned to supervisory personnel. Each person responsible for supervising the manufacture of dietary ingredients 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 ingredient 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 ingredients 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.

### 2.2.6 TRAINING

Training should be regularly conducted by qualified persons and should cover, at minimum, the particular operation(s) that the employee performs and cGMPs as it relates to the employee's functions. Training must also cover the principles of food hygiene and food safety, including the importance of employee health and personal hygiene, and, as appropriate to the dietary ingredient, the facility and the employee's assigned duties.

Training requirements should be specified (e.g., read and understand documents, instruction with trainer, on-the-job training). Training effectiveness should be periodically assessed. Training programs including on the job training should be re-assessed. Appropriate

documentation of any training must be retained by the company, including the date of the training, the type of training, the name of trainer if applicable, the person trained, and any assessment results (e.g., test results).

## 2.2.7 PERSONNEL RESPONSIBILITIES

The company management must take all reasonable measures and precautions to ensure the prevention of microbial contamination and to maintain hygienic practices.

**2.2.7.1 Preventing microbial contamination:** Any person who, by medical examination, by the person's acknowledgment, or by supervisory observation, is shown to have, or appears to have, an illness, infection, or open lesion, or has been exposed to communicable disease or any other abnormal source of microbial contamination that could result in microbial contamination of raw materials, other ingredients, in-process materials, dietary ingredients, or contact surfaces, must be excluded from working in any operations that may result in such contamination until the health concern no longer exists 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 health conditions to their supervisors.

**2.2.7.2 Hygienic practices:** All persons working in an operation in direct contact with raw materials, other ingredients, in-process materials, dietary ingredients, or food-contact surfaces must conform to hygienic practices to the extent necessary to protect against allergen cross-contact, microbial contamination, and other types of contamination of the dietary ingredient. These practices include the following:

- Wearing outer garments in a manner that protects against the contamination of raw materials, other ingredients, in-process materials, or dietary ingredients, or any food-contact surfaces
- Maintaining adequate personal cleanliness
- Removing cosmetics from parts of the body that may contact raw materials, other ingredients, in-process materials, dietary ingredients, or food-contact surfaces during performances of their duties
- Washing hands thoroughly (and sanitizing, if necessary, to protect against contamination with undesirable microorganisms) in an adequate hand-washing facility before starting work, as well as at any other time when the hands may have become soiled or contaminated
- Removing all unsecured jewelry and other objects that might fall into raw materials, other ingredients, in-process materials, dietary ingredients, equipment, or packaging materials, and removing hand jewelry that cannot be adequately sanitized during periods in which raw materials, other ingredients, in-process materials, or dietary ingredients 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 raw materials, other ingredients, in-process materials, dietary ingredients, or food-contact surfaces
- Maintaining gloves used in handling raw materials, other ingredients, in-process materials, or dietary ingredients in an intact, clean, and sanitary condition; the gloves must be of impermeable material if bare hands or gloves have the potential to come in contact with these materials during the performances of a person's duties
- Wearing hair nets, caps, beard covers, or other hair restraints when appropriate, such as when the raw material, in-process material, or ingredient is exposed, and in an effective manner
- Storing clothing or other personal belongings in areas separate from where raw materials, other ingredients, in-process materials, dietary ingredients, or any food-contact surface are exposed or where food-contact surfaces are washed
- Not eating food, chewing gum, drinking beverages, taking personal medication, or using tobacco products in areas where raw materials, other ingredients, in-process materials, dietary ingredients, or food-contact surfaces are exposed or where food-contact surfaces are washed
- Taking any other precautions necessary to protect against allergen cross-contact and contamination of raw materials, other ingredients, in-process materials, dietary ingredients, or food-contact surfaces with microorganisms, allergens, filth, foreign substances, or other extraneous materials, including perspiration, hair, cosmetics, tobacco, chemicals, and medicines applied to the skin. These precautions may include restricting individuals working in unit operations with known allergens from moving to non-allergen production areas, and/or color-coding of in-process allergen containing materials to differentiate them from non-allergen containing materials

## 2.3 Documentation and Records

### 2.3.1 GENERAL

Documentation can be viewed as the foundation of all quality systems, because clear, complete, and accurate records are essential to all operations and procedures. A guiding cGMP principle is that if it is not written down, it is not done. [Good Documentation Guidelines \(1029\)](#), which provides guidelines on good documentation practices for cGMP-regulated industries, should be followed.

All documents related to the manufacture of dietary ingredients must be initiated, prepared, reviewed, approved, distributed, and archived according to written procedures. Such documents can be in paper or electronic form.

When entries are made in records, these must be made legibly and indelibly in spaces provided for such entries, directly after performing the activities. Entries should identify the person making the entry, as well as the day and time when the entry was made. All dates must include the day, month, and year in a consistent and unambiguous format such as establishing a date format (e.g., DD-MM-YYYY) or spelling out the month. 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 and leave 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 for the correction.

### 2.3.2 CONTROL OF DOCUMENTATION

The issuance, revision, superseding, and withdrawal of all documents must be controlled by the 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 the following:

- Forms: content, revision, review
- 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 (paper and electronic) should be established with appropriate security, and documentation should be readily retrievable.

### 2.3.3 RECORDS RETENTION

The retention periods for these documents must be specified. Written records must be kept, at minimum, for 1 year past the retest or expiry date of the dietary ingredient associated with those records. Records must be kept as original records, as accurately reproduced copies (e.g., photocopies, microfilm, compact disc), or as electronic copies. All electronic records must comply with 21 CFR Part 11 (*Electronic Records; Electronic Signatures*).

All records or copies of records required by this general information chapter must be readily available during the retention period for inspection by the FDA when requested. If reduction techniques such as microfilming are used, suitable reader and photocopying equipment must be made readily available to the FDA.

## 2.4 Change Control

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

Any proposals for cGMP-relevant changes should be drafted, reviewed, and approved by the appropriate manufacturing units, as well as reviewed and approved by the quality unit(s).

The potential impact of the proposed change on the quality of the dietary ingredient should be evaluated. A classification procedure may help in determining the level of testing, validation, and documentation needed to justify changes to a validated process. Changes can be classified (e.g., as minor or major) depending on the nature and extent of the changes, and the effects these changes may impart on the process. Scientific judgment should determine what additional testing and validation studies are appropriate to justify a change in a validated process. When implementing approved changes, measures should be taken to ensure that all documents affected by the change are revised.

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

Dietary ingredient manufacturers should require their raw material suppliers or packagers to notify them of changes from established production process controls that can affect the quality of the dietary ingredient.

## 2.5 Deviations and Material Reviews

### 2.5.1 DEVIATIONS

Written procedures must be established and followed for documenting all deviations and for investigating deviations. Any deviation from established procedures and standards should be documented and explained. 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 deviations are investigated and resolved.

### 2.5.2 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 raw material, other ingredient, in-process material that is rejected, or reprocessing of a dietary ingredient 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 one of the following occurs:

- A specification is not met for a raw material, other ingredient, in-process material, packaging, labeling, dietary ingredient, a dietary ingredient received for packaging and labeling, or finished packaged and labeled dietary ingredient
- A batch deviates from the master production and control record, including when any step is not completed and any deviation from specifications occurs
- Any unanticipated occurrence during manufacturing operations adulterates or could lead to adulteration of the raw material, other ingredient, in-process material, dietary ingredient, or packaging, or could lead to the use of a label not specified in the master

production and control record

- Calibration of an instrument or control suggests a problem may have resulted in a failure to ensure the quality of a batch or batches of a dietary ingredient
- A dietary ingredient is returned

Quality unit personnel must reject the raw material, other ingredient, in-process material, dietary ingredient, packaging, or labeling when an established specification is not met or when a deviation or unanticipated occurrence during the batch production and in-process control system results in or could lead to adulteration of the product. However, the quality unit can approve a treatment, an in-process adjustment, or a reprocessing to correct the deviation or occurrence, ensuring that the quality of the final dietary ingredient and that its packaging and labeling meets the specifications of the master production and control 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 the following:

- Description of the specific deviation or unanticipated occurrence
- Description of the root cause investigation
- Evaluation of whether the deviation or unanticipated occurrence has resulted in or could lead to a failure to ensure the quality of the dietary ingredient or failure to package and label the dietary ingredient as specified in the master production and control 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, in-process adjustment, or reprocessing 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
- Signatures of individual(s) who are designated to perform quality unit operations and 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 and control record.

## 2.6 Corrective and Preventative Actions

Corrective Actions and Preventative Actions (CAPA) programs are important to continuous improvement of the quality management system. The CAPA operating system is an essential governance document by which personnel plan and implement control to mitigate and control failures within the quality management systems. CAPAs may rise 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 and nonconformities, including out-of-specification (OOS) laboratory results, and corrective and/or preventive action(s). 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, corrective, 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. See 2.7.4.2 *Corrective actions and correction procedures* for further details regarding corrective actions and correction procedures as they apply to the FSP.

A [Glossary](#) that includes CAPA terms (i.e., corrective action, preventive action, remedial (short-term) action, nonconformity, deviation, root cause) is presented at the end of the chapter.

## 2.7 Hazard Analysis and Risk-Based Preventive Controls (HARPC)

### 2.7.1 FOOD SAFETY PLAN (FSP)

The HARPC include the requirement to prepare and implement a written FSP that is overseen by one or more preventive controls-qualified individuals. The scope of HARPC/FSP includes evaluating hazards that could affect food safety; implementing preventive steps or controls to minimize or prevent hazards; monitoring the controls to ensure that they work; maintaining records of monitoring; and specifying what actions will be taken to correct problems that arise, including a recall plan for the dietary ingredient. The FDA's draft guidance *Hazard Analysis and Risk-Based Preventive Controls for Human Food: Guidance for Industry* should be consulted.

The contents of the written FSP must include the following:

- Hazard analysis
- Preventive controls
- Supply chain controls
- Recall plan
- Monitoring implementation of preventive controls
- Corrective actions and correction procedures
- Verification and validation procedures
- Associated records

## 2.7.2 HAZARD ANALYSIS

A hazard analysis must be conducted to identify and evaluate known or reasonably foreseeable hazards for each type of dietary ingredient manufactured, processed, packed, or held at the facility to determine whether there are any hazards requiring preventive control. This hazard analysis is based on experience, illness data, scientific reports, and other information.

Hazard identification must include known or reasonably foreseeable hazards, such as the following:

- Biological hazards, including microbiological hazards such as parasites, environmental pathogens, and other pathogens
- Chemical hazards, including radiological hazards, substances such as pesticides and drug residues, natural toxins, decomposition, unapproved or color additives, and food allergens
- Physical hazards, such as stones, glass, and metal fragments
- Hazards that may be present in the dietary ingredient for any of the following reasons:
  - The hazard occurs naturally
  - The hazard may be introduced unintentionally
  - The hazard may be introduced intentionally for the purpose of economic gain

The identified hazards must be evaluated to assess the severity of the illness or injury if the hazards were to occur and the probability that the hazard will occur in the absence of preventive controls. Hazard evaluation must include environmental pathogens whenever a dietary ingredient is exposed to the environment prior to packaging and the packaged dietary ingredient does not receive a treatment or another control measure, such as formulations with antimicrobial properties that would significantly minimize or reduce the likelihood for the presence of pathogenic microorganisms. The hazard evaluation analysis also must consider the effect of the following factors on the safety of the finished dietary ingredient for the intended consumer:

- Physical and chemical properties of the dietary ingredient (e.g., water activity, pH)
- Formulation of the dietary ingredient
- Condition, function, and design of facility and equipment
- Raw materials and other ingredients
- Transportation practices
- Manufacturing/processing procedures
- Packaging activities and labeling activities
- Storage and distribution
- Intended or reasonably foreseeable use
- Sanitation, including employee hygiene
- Any other relevant factors, such as the temporal (e.g., weather-related) nature of some hazards (e.g., levels of some natural toxins)

## 2.7.3 PREVENTIVE CONTROLS

Preventive controls must be identified and implemented to provide assurances that any hazards requiring a preventive control will be significantly minimized or prevented and the dietary ingredient manufactured, processed, packed, or held by the facility will not be adulterated or misbranded. Preventive controls must be written. Preventive controls include controls at any critical control points (CCPs) and other controls appropriate for food safety.

Preventive controls include the following, as appropriate to the facility:

- Process controls
- Food allergen controls
- Sanitation controls
- Supply-chain controls
- Recall plan

**2.7.3.1 Process controls:** These include procedures, practices, and processes to ensure the control of parameters during operations such as heat processing, acidifying, irradiating, and refrigerating foods. As appropriate to the nature of the applicable control and its role in the facility's food safety system, process controls must include parameters associated with the control of the hazard and the maximum or minimum value, or combination of values, to which any biological, chemical, or physical parameter must be controlled to significantly minimize or prevent a hazard. Where practical, dietary ingredient manufacturers should employ process analytical technologies such as electronic metal detection to mitigate the risk of hazards.

**2.7.3.2 Food allergen controls:** These include procedures, practices, and processes to control food allergens. As appropriate, food allergen controls must include those procedures, practices, and processes employed for ensuring the protection of food from allergen cross-contact, including during storage, handling, and use; and labeling the finished food, including ensuring that the finished food is not misbranded.

**2.7.3.3 Sanitation controls:** These include procedures, practices, and processes to ensure that the facility is maintained in a sanitary condition adequate to significantly minimize or prevent hazards such as environmental pathogens, biological hazards due to employee handling, and food allergen hazards. As appropriate to the facility and the dietary ingredient, sanitation controls must include procedures, practices, and processes for the cleanliness of food-contact surfaces, including food-contact surfaces of utensils and equipment, and prevention of allergen cross-contact and cross-contamination from insanitary objects, from personnel to food, food packaging material, and other food-contact surfaces, and from raw product to processed product.

**2.7.3.4 Supply-chain controls:** When dietary ingredient manufacturers who receive the raw materials and other ingredients identify a hazard that requires a supply-chain-applied control, a written risk-based supply-chain control program must be established and implemented for those raw materials and other ingredients. The supply-chain program must provide assurance that a hazard requiring a supply-chain-applied control has been significantly minimized or prevented.

If the receiving facility is an importer that is in compliance with the foreign supplier verification program requirements in 21 CFR Part 1, Subpart L, and that has documentation of verification activities conducted in 21 CFR 1.506(e) (which provides assurance that the hazards requiring a supply-chain-applied control for the raw material or other ingredient have been significantly minimized or prevented), it does not need to conduct supplier verification activities for that raw material or other ingredient.

When a supply-chain-applied control is applied by an entity other than the dietary ingredient manufacturer's supplier (e.g., a raw material or other ingredient manufacturer applies controls under different management than the supplier), the dietary ingredient manufacturer must verify the supply-chain control or obtain documentation of appropriate verification activity from the 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 FSP.

The supply-chain control program must include the following:

- Using approved suppliers and documenting that approval before receiving raw materials and other ingredients from those suppliers
  - Written procedures for receiving raw materials and other ingredients must be established and followed and must ensure that raw materials and other ingredients are received only from approved suppliers (or, when necessary and appropriate, on a temporary basis from unapproved suppliers whose raw materials and other ingredients are subjected to adequate verification activities before acceptance for use)
  - Use of the written procedures for receiving raw materials and other ingredients must be documented
- Determining appropriate supplier verification activities, including determining the frequency of conducting the activity by considering the following:
  - The hazard analysis of the raw material or other ingredient, including the nature of the hazard controlled before receipt of the raw material or other ingredient
  - The entity or entities that will be applying controls for the hazards requiring a supply-chain-applied control
  - Supplier performance, including the following:
    - The supplier's procedures, processes, and practices inherent to the hazards associated with the raw material and other ingredients
    - Applicable FDA food safety regulations and information relevant to the supplier's compliance with those regulations, including an FDA warning letter or import alert relating to the safety of the raw material and other ingredients, and other FDA compliance actions related to food safety (or, when applicable, relevant laws and regulations of a country whose food safety system FDA has officially recognized as comparable or has determined to be equivalent to that of the United States, and information relevant to the supplier's compliance with those laws and regulations)
    - The supplier's food safety history relevant to the raw materials and other ingredients that the manufacturer receives from the supplier, including available information about results from testing raw materials and other ingredients for hazards, audit results relating to the safety of the raw material and other ingredients, and responsiveness of the supplier in correcting problems
  - Any other factors as appropriate and necessary, such as storage and transportation practices
- Conducting one or more supplier verification activities as determined to be appropriate for raw materials and other ingredients, and approving each supplier before using the raw materials and other ingredients
  - Risk-based supplier verification activities may include the following:
    - On-site audits
    - Sampling and testing of raw materials and other ingredients to verify the accuracy of information on the supplier certificate of analysis
    - Review of supplier's relevant food safety records
    - Other appropriate supplier verification activities based on supplier performance and the risk associated with the raw materials and other ingredients
  - When a hazard in a raw material or other ingredient will be controlled by the supplier and is one for which there is a reasonable probability that exposure will result in serious adverse health consequences or death to humans, the appropriate supplier verification activity is an on-site audit of the supplier, which must be conducted annually unless there is a written determination that other verification activities and/or less frequent on-site auditing of the supplier provide adequate assurance that the hazards are controlled
  - There must not be any financial conflicts of interests that influence the results of the verification activities, and payment must not be related to the results of the activity

- Taking and documenting prompt corrective measures to ensure that raw materials and other ingredients from the supplier do not cause the dietary ingredient to be adulterated or misbranded, if the manufacturer has identified through auditing, verification testing, document review, relevant consumers, and customer or other complaints that the supplier is not controlling hazards requiring a supply-chain-applied control
- Documenting supplier qualification activities

2.7.3.4.1 *On-site audit*: An on-site audit of a supplier must be performed by a qualified auditor. If the raw material or other ingredient at the supplier is subject to one or more FDA food safety regulations, an on-site audit must consider such regulations and include a review of the supplier's written plan (e.g., HACCP plan or other FSP), if any, and its implementation for the hazard being controlled (or, when applicable, an on-site audit may consider relevant laws and regulations of a country whose food safety system the FDA has officially recognized as comparable or has determined to be equivalent to that of the United States).

One of the following may be substituted for an on-site audit, provided that the inspection was conducted within 1 year of the date that the on-site audit would have been required to be conducted:

- The written results of an appropriate inspection of the supplier for compliance with applicable FDA food safety regulations conducted and reported by the FDA, by representatives of other federal agencies (such as the US Department of Agriculture), or by representatives of state, local, tribal, or territorial agencies
- For a foreign supplier, the written results of an inspection by the FDA or the food safety authority of a country whose food safety system the FDA has officially recognized as comparable or has determined to be equivalent to that of the United States
  - For inspections conducted by the food safety authority of a country, the raw material or other ingredient that is the subject of the on-site audit must be within the scope of the official recognition or equivalence determination, and the foreign supplier must be in and under the regulatory oversight of that country.

An on-site audit is not subject to the requirements in 21 CFR Part 1, Subpart M, if it is solely conducted to meet the requirements of the manufacturer's supply-chain control program by an audit agent of a certification body accredited in accordance with those regulations.

2.7.3.4.2 *Responsibilities of the receiving facility*: The receiving facility must approve suppliers. The receiving facility must determine and conduct appropriate supplier verification activities and satisfy all supply-chain-program documentation requirements.

An entity other than the receiving facility may do any of the following provided that the receiving facility reviews and assesses the entity's applicable documentation and documents that review and assessment:

- Establish written procedures for receiving raw materials and other ingredients by the entity
- Document that written procedures for receiving raw materials and other ingredients are being followed by the entity
- Determine and/or conduct the appropriate supplier verification activities with appropriate documentation

As a supplier verification activity for a particular lot of product, the supplier may conduct and document sampling and testing of raw materials and other ingredients for the hazard controlled by the supplier and provide such documentation to the receiving facility, provided that the receiving facility reviews and assesses that documentation and maintains a record of that review and assessment.

A receiving facility may not accept any of the following as a supplier verification activity:

- A determination by its supplier of the appropriate supplier verification activities for that supplier
- An audit conducted by its supplier
- A supplier-conducted review of that supplier's own relevant food safety records

The requirements of this section do not prohibit a receiving facility from relying on an audit provided by its supplier when the audit was conducted by a third-party qualified auditor.

2.7.3.4.3 *Supply-chain program documentation and records*: The manufacturer receiving raw materials and other ingredients must document and review the following records as applicable to its supply-chain program:

- The written supply-chain program
- Documentation that a receiving facility that is an importer is in compliance with the foreign supplier verification program requirements in 21 CFR part 1, subpart L, including documentation of verification activities in 21 CFR 1.506(e)
- Documentation of the approval of a supplier
- Written procedures for receiving raw materials and other ingredients
- Documentation demonstrating use of the written procedures for receiving raw materials and other ingredients
- Documentation of the determination of the appropriate supplier verification activities for raw materials and other ingredients
- Documentation of the conduct of an on-site audit, which must include:
  - The name of the supplier subject to the on-site audit
  - Documentation of audit procedures
  - The dates the audit was conducted
  - The conclusions of the audit
  - Corrective actions taken in response to significant deficiencies identified during the audit
  - Documentation that the audit was conducted by a qualified auditor
- Documentation of sampling and testing conducted as a supplier verification activity, which must include:
  - Identification of the raw material or other ingredient tested (including lot number) and the number of samples tested
  - Identification of the test(s) conducted, including the analytical method(s) used

- The date(s) on which the test(s) were conducted and the date of the report
- The results of the testing
- Corrective actions taken in response to detection of hazards
- Information identifying the laboratory conducting the testing
- Documentation of the review of the supplier's relevant food safety records, which must include:
  - The name of the supplier whose records were reviewed
  - The date(s) of the review
  - The general nature of the records reviewed
  - The conclusions of the review
  - Corrective actions taken in response to significant deficiencies identified during the review
- Documentation of other appropriate supplier verification activities based on the supplier performance and the risk associated with the raw material or other ingredient
- Documentation of any determination that verification activities other than an on-site audit and/or less frequent on-site auditing of a supplier provide adequate assurance that the hazards are controlled when the supplier controls a hazard in a raw material or other ingredient and that hazard is one for which exposure could probably result in serious adverse health consequences or death to humans
- The written results of an appropriate inspection of the supplier for compliance with applicable FDA food safety regulations by the FDA, by representatives of other federal agencies (such as the US Department of Agriculture), or by representatives from state, local, tribal, or territorial agencies, or the food safety authority of another country when the results of such an inspection is substituted for an on-site audit
- Documentation of actions taken with respect to supplier non-conformance
- Documentation of verification of a supply-chain-applied control applied by an entity other than the receiving facility's supplier
- When applicable, documentation of the receiving facility's review assessment, which could include:
  - Applicable documentation from an entity other than the receiving facility:
    - Of written procedures for receiving raw materials and other ingredients being followed
    - Of the determination of the appropriate supplier verification activities for raw materials and other ingredients
    - Of conducting the appropriate supplier verification activities for raw materials and other ingredients
    - Of the verification activities when a supply-chain-applied control is applied by an entity other than the receiving facility's supplier
  - Applicable documentation from its supplier:
    - Of the results of sampling and testing conducted by the supplier
    - Of the results of an audit conducted by a third-party qualified auditor

Supplier verification activities must be documented. Formal reports should be generated for each raw material or other ingredient from each supplier summarizing initial supplier verification activities and analyses, and plans and schedule for continuous monitoring. An approved list of raw materials, other ingredients, and suppliers should be readily available to staff. A unique material item code should be assigned for each material from each supplier; however, the manufacturer may identify equivalencies between the same raw materials and other ingredients from different suppliers as long as they meet the same critical specifications 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.

**2.7.3.5 Recall plan:** For dietary ingredients with a hazard requiring a preventive control, the manufacturer must establish a written recall plan for the dietary ingredient. The written recall plan must include procedures that describe the steps to be taken and assign responsibility for taking those steps and to perform the following actions as appropriate to the facility:

- Directly notify the direct consignees of the dietary ingredient being recalled, including how to return or dispose of the affected dietary ingredient
- Notify the public about any hazard presented by the dietary ingredient when appropriate to protect public health
- Conduct effectiveness checks to verify that the recall is carried out
- Appropriately dispose of the recalled dietary ingredient (e.g., through reprocessing, reworking, diverting to a use that does not present a safety concern, or destroying the dietary ingredient)

A written procedure should define the circumstances under which recall of a dietary ingredient 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 ingredient should be treated. If the event of a health hazard is not self-evident, then an independent health hazard assessment by a qualified individual or organization should be conducted to determine the depth and scope of a recall. In the event of a serious or potentially life-threatening situation, local, national, and/or international regulatory authorities should be informed, and their advice sought to ensure regulations are properly followed and executed for disposition of the recalled article.

Mock recalls should be performed annually.

**2.7.3.6 Other controls:** Other controls include any other procedure, practice, and process necessary to ensure that food will not be adulterated or misbranded; examples of other controls include hygiene training and other good cGMPs.

## 2.7.4 PREVENTIVE CONTROL MANAGEMENT

Preventive controls are subject to the following preventive control management components as appropriate to ensure the effectiveness of the controls while considering their nature and their role in the facility's food safety system:

- Monitoring
- Corrective actions and corrections
- Verification

The supply-chain program is subject to the following preventive control management component as appropriate to ensure the effectiveness of the supply-chain program while considering the nature of the hazard controlled before receipt of the raw material or other ingredient:

- Corrective actions and corrections that consider the nature of any supplier non-conformance:
  - Review of records
  - Re-analysis

**2.7.4.1 Monitoring:** As appropriate to the nature of the preventive controls and their role in the facility's food safety system, written procedures must be established and implemented and include the frequency with which they are to be performed for monitoring the preventive controls. Preventive controls must be monitored with adequate frequency to provide assurance that they are consistently performed. The monitoring of preventive controls must be documented in records that are subject to verification and records review.

**2.7.4.2 Corrective actions and correction procedures:** As appropriate to the nature of the hazard and the nature of the preventive controls, the manufacturer must establish and implement written corrective action procedures that must be taken if preventive controls are not properly implemented, including procedures to address, for the presence of the following hazards:

- The presence of a pathogen or appropriate indicator organism detected as a result of product testing
- The presence of an environmental pathogen or appropriate indicator organism detected through environmental monitoring

The corrective action procedures must describe the steps to be taken to ensure that:

- Appropriate action is taken to identify and correct a problem that has occurred with implementation of a preventive control
- Appropriate action is taken when necessary to reduce the likelihood that the problem will reoccur
- All affected dietary ingredients are evaluated for safety
- All affected dietary ingredients are prevented from entering commerce, if the manufacturer cannot ensure that the affected dietary ingredient is not adulterated or misbranded

The manufacturer must follow these steps and, if appropriate, re-analyze the FSP to determine whether modification of the FSP is required if any of the following circumstances occur:

- A preventive control is not properly implemented and a corrective action procedure has not been established
- A preventive control, combination of preventive controls, or the FSP is found to be ineffective
- A review of records finds that the records are not complete, the activities conducted did not occur in accordance with the FSP, or appropriate decisions were not made about corrective actions

All corrective actions (and corrections, when appropriate) taken must be documented in records that are subject to verification and records review.

**2.7.4.3 Verification activities:** Verification activities must include the following preventive control management components as appropriate to the nature of the preventive controls and their role in the facility's food safety system:

- Validation
- Verification that monitoring is being conducted as required in 2.7.4.1 *Monitoring*
- Verification that appropriate decisions about corrective actions are being made as required in 2.7.4.2 *Corrective actions and correction procedures*
- Verification of implementation and effectiveness
- Re-analysis

All verification activities must be documented in records and are subject to review.

**2.7.4.3.1 Validation:** The manufacturer must validate that the preventive controls identified and implemented are adequate to control the hazard as appropriate to the nature of the controls and their role in the facility's food safety system. The validation of the preventive controls must be performed (or overseen) by a preventive controls-qualified individual at the following times:

- Prior to implementation of the FSP
- When necessary to demonstrate the control measures can be implemented as designed (within 90 calendar days, or within a reasonable justifiable time frame after production of the applicable dietary ingredient first begins)
- Whenever a change to a control measure or combination of control measures could affect whether the control measure or combination of control measures, when properly implemented, will effectively control the hazards
- Whenever a re-analysis of the FSP reveals the need to do so

The validation of the preventive controls must include obtaining and evaluating scientific and technical evidence (or, when such evidence is not available or is inadequate, conducting studies) to determine whether the preventive controls, when properly implemented, will effectively control the hazards.

The manufacturer does not need to validate the food allergen controls, the sanitation controls, the recall plan, the supply-chain controls, and other preventive controls if the preventive controls-qualified individual prepares (or oversees the preparation of) a written justification that validation is not applicable based on factors such as the nature of the hazard and the nature of the preventive control and its role in the facility's food safety system.

**2.7.4.3.2 Verification of implementation and effectiveness:** The manufacturer must verify that the preventive controls are consistently implemented and are effectively and significantly minimizing or preventing the hazards by conducting the following activities as appropriate to the facility, the dietary ingredient, and the nature of the preventive controls and their role in the facility's food safety system:

- Calibration of process monitoring instruments and verification instruments (or checking them for accuracy)
- Product testing for a pathogen (or appropriate indicator organism) or another hazard
- Environmental monitoring for an environmental pathogen or for an appropriate indicator organism
- Other activities appropriate for verification of implementation and effectiveness
- Review of the following records within the specified time frames by (or under the oversight of) a preventive controls-qualified individual to ensure that the records are complete, the activities reflected in the records occurred in accordance with the FSP, the preventive controls are effective, and appropriate decisions were made about corrective actions:
  - Records of monitoring and corrective action records within 7 working days after the records are created or within a reasonable time frame, provided that the preventive controls-qualified individual prepares (or oversees the preparation of) a written justification for a time frame that exceeds 7 working days. All records should be reviewed and approved by a qualified individual before the products are released in the market
  - Records of calibration, testing (e.g., product testing, environmental monitoring), supplier and supply-chain verification activities, and other verification activities within a reasonable time after the records are created

As appropriate to the facility, the food, the nature of the preventive control, and the role of the preventive control in the facility's food safety system, the manufacturer must establish and implement written procedures for the following activities:

- The method and frequency of calibrating process monitoring instruments and verification instruments (or checking them for accuracy)
- Product testing procedures that must:
  - Be scientifically valid
  - Identify the test microorganism(s) or other analytes
  - Specify the procedures for identifying samples, including their relationship to specific lots of product
  - Include the procedures for sampling, including the number of samples and the sampling frequency
  - Identify the test(s) conducted, including the analytical method(s) used
  - Identify the laboratory conducting the testing
  - Include the corrective action procedures
- Environmental monitoring procedures that must:
  - Be scientifically valid and based on risk management procedures
  - Identify the test microorganism(s)
  - Identify the locations from which samples will be collected and the number of sites to be tested during routine environmental monitoring (the number and location of sampling sites must be adequate to determine whether preventive controls are effective)
  - Identify the timing and frequency for collecting and testing samples (the timing and frequency for collecting and testing samples must be adequate to determine whether preventive controls are effective)
  - Identify the test(s) conducted, including the analytical method(s) used
  - Identify the laboratory conducting the testing
  - Include the corrective action procedures

**2.7.4.3.3 Re-analysis:** The manufacturer must conduct a re-analysis of the FSP in its entirety once every 3 years. In addition, the manufacturer must conduct a re-analysis either in its entirety or of the affected portion of the FSP when one of the following occurs:

- Whenever a significant change in the activities conducted at the facility creates a reasonable potential for a new hazard or creates a significant increase in a previously identified hazard
- Whenever the manufacturer becomes aware of new information about potential hazards associated with the dietary ingredient
- Whenever appropriate after an unanticipated food safety problem
- Whenever the manufacturer finds that a preventive control, combination of preventative controls, or the FSP in its entirety is ineffective
- Whenever the FDA determines it is necessary to respond to new hazards and developments in scientific understanding

The manufacturer must complete the re-analysis and validate as appropriate to the nature of the preventive controls and their role in the facility's food safety system any additional preventive controls needed to address the hazard identified in one of the following time

frames:

- Before any change in activities (including any change in preventive control) at the facility is operative
- When necessary to demonstrate the control measures can be implemented as designed within one of the following:
  - 90 calendar days after production of the applicable dietary ingredient
  - A reasonable time frame, provided that the preventive controls-qualified individual prepares (or oversees the preparation of) a written justification for a time frame that exceeds 90 calendar days after production of the applicable dietary ingredient first begins

The manufacturer must either revise the written FSP if a significant change in the activities conducted at the facility creates a reasonable potential for a new hazard or a significant increase in a previously identified hazard, or document the basis for the conclusion that no revisions are needed. A preventive controls-qualified individual must perform (or oversee) the re-analysis and revisions to the FSP.

### 2.7.5 HARP IMPLEMENTATION RECORDS

The manufacturer must establish and maintain the following records documenting implementation of the FSP:

- Records that document the monitoring of preventive controls
- Records that document corrective actions
- Records that document verification, including, as applicable, those related to:
  - Validation
  - Verification of monitoring
  - Verification of corrective actions
  - Calibration of process monitoring and verification instruments
  - Product testing
  - Environmental monitoring
  - Records review
  - Re-analysis
- Records that document the supply-chain program
- Records that document applicable training for the preventive controls-qualified individual and the qualified auditor

## 2.8 Contract Manufacturers and Contract Laboratories

All contract manufacturers and contract laboratories should comply with the requirements of this chapter. Special consideration should be given to the prevention of allergen cross-contact and cross-contamination and to maintaining traceability.

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

A written and approved contract or quality agreement should define in detail the cGMP responsibilities, including the quality measures, of each party. The contract acceptor should permit the contract giver to audit the contract acceptor's facilities for compliance with cGMPs. When subcontracting is allowed, the contract acceptor should use a third party for 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 is informed and approves the changes.

## 2.9 Complaints

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

Complaint records should include the following:

- Name, address, and phone number of complainant
- Name of dietary ingredient, item code, and lot number
- Nature of the complaint, including how the product was used if known
- Date 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 complainant, including the date the response was sent
- Final findings and decision on product lot
- 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 ingredient 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.

## 2.10 Internal (Self-Inspection) Audits

To verify compliance with the requirements of this 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. Internal audits also should verify that computer systems with an audit trail feature have it enabled.

## 2.11 Product Quality Reviews

Regular quality reviews of dietary ingredients should be conducted annually or by using a matrix and bracketing approach on a rotation cycle over a 3-year period with the objective of verifying the consistency of the manufacturing process.

Such review should normally include a review of the following:

- Critical dietary ingredient test results
- All batches that failed to meet established specification(s)
- Deviations or nonconformities and related investigations
- Adequacy of corrective actions
- Changes to the manufacturing process and analytical test methods
- Results of the stability monitoring program
- 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.

## 2.12 Quality Management Documentation

The following documentation must be made and kept for fulfilling the requirements of the quality management system (see 1. *General Provisions*).

### 2.12.1 WRITTEN PROCEDURES

Written procedures must be established and followed for the following:

- Creating and maintaining job position descriptions and 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 an FSP
- Implementing a supplier-chain control program
- Handling recalls
- Implementing a contract (manufacturing and laboratory) services program
- Implementing a complaint handling program
- Conducting internal audits
- Conducting product quality reviews

### 2.12.2 RECORDS

Records must meet the following standards:

- Be kept as original records, true copies (e.g., photocopies, pictures, scanned copies, microfilm, microfiche, or other accurate reproductions of the original records), or electronic records including associated metadata
- Contain the actual values and observations obtained during monitoring and, as appropriate, during verification activities
- Be accurate, indelible, and legible
- Be created concurrently with performance of the activity documented
- Be as detailed as necessary to provide history of work performed
- Include the following information:
  - Information adequate to identify the plant or facility (e.g., the name and when necessary the location of the plant or facility)
  - The date and, when appropriate, the time of the activity documented
  - The signature or initials of the person performing the activity
  - When appropriate, the identity of the product and the lot code

Records must be made and kept for the following:

- Organizational chart, job position descriptions, and curriculum vitae for all key management staff in manufacturing and quality operations
- Training, including the date of the training, the type of training, name of trainer if applicable, the person(s) trained, content of the training or reference to a document that describes the content, and any assessment results (e.g., test results)
- List and copies of current standard operating procedures, manufacturing instructions, and standard test methods
- List and reports of changes that affect the production and quality of dietary ingredients
- List and reports of unanticipated occurrences and deviations from approved instructions or established standards
- List and reports of material reviews
- List and reports of corrective actions and preventative actions taken
- List of approved suppliers of raw materials, other ingredients, packaging materials and labeling, and corresponding supplier qualification evaluation reports
- List of approved suppliers of manufacturing and laboratory services, including any provided service such as pest control and metrology, and of corresponding evaluation reports and related quality agreements
- List of complaints and corresponding investigation reports
- Recall and mock recall reports
- Internal (self-inspection) audit schedule and reports
- Product quality review reports

The owner, operator, or agent in charge of the facility must sign and date the FSP upon initial completion and upon any modification.

All records must be retained at the plant or facility for at least 2 years after the date they were prepared. Records that relate to the general adequacy of the equipment or processes being used by a facility, including the results of scientific studies and evaluations, must be retained by the facility for at least 2 years after their use is discontinued (e.g., because the facility has updated the written FSP or records that document validation of the written FSP).

Except for the FSP, off-site storage of records is permitted if such records can be retrieved and provided on-site within 24 h of request for official review. The FSP must remain on-site, except when the plant or facility is closed for a prolonged period, in which case the FSP may be transferred to some other reasonably accessible location but must be returned to the plant or facility within 24 h for official review upon request. Electronic records are on-site if they are accessible from an on-site location.

Existing records (e.g., records kept to comply with other federal, state, or local regulations, or for any other reason) do not need to be duplicated if they contain all of the required information and satisfy applicable requirements. Existing records may be supplemented as necessary to include all required information and satisfy the applicable requirements. The information required does not need to be kept in one set of records. If existing records contain some of the required information, any new information required may be kept either separately or combined with the existing records.

### **3. PHYSICAL PLANT AND EQUIPMENT**

#### **3.1 Grounds Maintenance**

The grounds around the physical plant must be kept in a condition that protects against the contamination of raw materials, other ingredients, in-process material, dietary ingredients, and food-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 become a source of contamination in areas where raw materials, other ingredients, in-process material, dietary ingredients, or food-contact surfaces are exposed
- Adequately draining areas that may contribute to the contamination of raw materials, other ingredients, in-process materials, dietary ingredients, or food-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 raw materials, other ingredients, in-process materials, dietary ingredients, or food-contact surfaces are exposed
- Exercising care if the physical plant grounds are bordered by grounds not under the operator's control and not maintained in the aforementioned manner, using inspection, extermination, or other means to exclude pests, dirt, filth, or any other extraneous materials that may be a source of contamination

#### **3.2 Physical Plant Design**

Any physical plant used in the manufacture of dietary ingredients 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-ups of materials.

The physical plant must take adequate precautions to reduce the potential for allergen cross-contact and for contamination of materials and food-contact surfaces with microorganisms, chemicals, filth, and other extraneous materials. The potential for allergen cross-contact and for contamination may be reduced by adequate food safety controls and operating practices or effective design, including the separation of operations in which allergen cross-contact and contamination are 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.

The flow of materials and personnel throughout the physical plant should be designed to prevent contamination and mix-ups of materials.

### 3.2.1 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 and spatial to prevent contamination or allergen cross-contact and mix-ups of raw materials, other ingredients, in-process materials, dietary ingredients, and 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, as appropriate
- Physically separating allergen-containing materials from non-allergen-containing 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 ingredients and other foods, cosmetics, and pharmaceutical products
- Cleaning and sanitizing food-contact surfaces as necessary
- Performing and separating chemical and microbiological laboratory analyses and holding of laboratory samples and supplies

Laboratory areas/operations normally should 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.

### 3.2.2 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 by condensation
- 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 food-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 food-contact surfaces
- Equipment that controls air pressure, temperature, and humidity as needed to ensure the quality of the dietary ingredient; attention should be given to areas where raw materials, other ingredients, in-process materials, and dietary ingredients 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 or food-contact surfaces with clothing or personal contact
- Adequate lighting in all areas where material is examined, processed, or held, or where food-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 using, for example, protective coverings; placement in areas where harborage for pests can be eliminated over and around the vessels and where staff can check regularly for pests, pest infestation, filth, or any other extraneous materials; or use of skimming equipment

## 3.3 Physical Plant Sanitation and Facilities

The physical plant must be kept clean and sanitary and maintained in repair adequate to prevent materials and contact surfaces from becoming contaminated. Cleaning and sanitizing of utensils and equipment must be conducted in a manner that protects against allergen cross-contact and against contamination of food, food-contact surfaces, or food-packaging materials.

Overall sanitation of the physical plant must be under the supervision of one or more competent individuals assigned responsibility for this function.

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.

The physical plant must be equipped with adequate sanitary facilities and accommodations including water supply, plumbing, sewage disposal, toilet facilities, hand-washing facilities, and rubbish and offal disposal.

Utilities that could affect dietary ingredient quality (e.g., steam, gases, compressed air, and 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.

### 3.3.1 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 or with an examination of these substances for contamination. Toxic materials must not be used or held in the physical plant in which raw materials, other ingredients, in-process materials, dietary ingredients, and food-contact surfaces are manufactured and/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 for use in the physical plant's operations. Toxic materials must be identified and held in a manner that protects against contamination of raw materials, other ingredients, in-process materials, dietary ingredients, and food-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 ingredients 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.

### 3.3.2 PEST CONTROL

No animals or pests must be allowed in any area of the physical plant. Guard, guide, or pest-detecting dogs may be allowed in some areas of a plant if the presence of the dogs is unlikely to result in the contamination of materials or food-contact surfaces. Effective measures must be taken to exclude pests from the physical plant and to protect against contamination of materials and food-contact surfaces on the premises by pests. The use of pesticides, such as insecticides, fumigants, fungicides, or rodenticides, is permitted only if precautions and restrictions are taken to protect against the contamination of raw materials, other ingredients, in-process materials, dietary ingredients, and food-contact surfaces. Pesticides should be registered and used in accordance with the Federal Insecticide, Fungicide, and Rodenticide Act (7 USC §136 et seq.).

### 3.3.3 SANITATION OF CONTACT SURFACES

All food-contact surfaces including utensils and equipment must be cleaned as frequently as necessary to protect against allergen cross-contact and against contamination of dietary ingredients.

Food-contact surfaces used for manufacturing/processing, packing, or holding low-moisture food must be in a clean, dry, and sanitary condition before use. When the surfaces are wet-cleaned, they must, when necessary, be sanitized and thoroughly dried before subsequent use.

In wet processing, when cleaning is necessary to protect against allergen cross-contact or the introduction of microorganisms into the dietary ingredient, all food-contact surfaces must be cleaned and sanitized before use and after any interruption during which food-contact surfaces may have become contaminated. When equipment and utensils are used in a continuous production operation, the utensils and food-contact surfaces of the equipment must be cleaned and sanitized, as necessary, to prevent contamination.

Single-service articles (e.g., utensils intended for one-time use, paper cups, and paper towels) must be stored, handled, and disposed of in a manner that protects against allergen cross-contact and against contamination of food and food-contact surfaces.

Non-food-contact surfaces of equipment used in the operation of the physical plant must be cleaned in a manner and as frequently as necessary to protect against allergen cross-contact and against contamination of food, food-contact surfaces, and food-packaging materials.

Cleaned and sanitized portable equipment with food-contact surfaces and utensils must be stored in a location and manner that protects food-contact surfaces from allergen cross-contact and contamination.

### 3.3.4 WATER SUPPLY

Potable water at a suitable temperature, and under pressure as needed, must be supplied in all areas where required for the processing of food; for cleaning of equipment, utensils, and food-packaging materials; or for staff sanitary facilities. The potable water must be supplied in a plumbing system free of defects and that protects against contamination or undesirable chemical reaction of raw materials, other ingredients, in-process materials, dietary ingredients, and food-contact surfaces. Any water that contacts food, food-contact surfaces, or food packaging materials must be safe and of adequate sanitary quality.

Potable water must meet, at minimum, all the requirements for drinking water promulgated in the US Environmental Protection Agency's National Primary Drinking Water Regulations (40 CFR Part 141), and any applicable state and local drinking water requirements that are more stringent. For manufacturers outside the United States, 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](#).

When 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 criteria.

### 3.3.5 PLUMBING

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

- Carry adequate amounts of water to the required locations throughout the physical plant
- Properly convey sewage and liquid disposable waste from the physical plant
- Avoid constituting a source of contamination to food, water supplies, and contact surfaces, 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
- 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 ingredients, 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.

### 3.3.6 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 in an adequate sewage system or through other adequate means. 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.

When raw materials, other ingredients, or refuse are unprotected, they must not be handled simultaneously in a receiving, loading, or shipping area if that handling could result in allergen cross-contact or contaminated food.

### 3.3.7 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. Hand-washing facilities must be designed to ensure that an employee's hands are not a source of contamination of materials and contact surfaces. The facilities must be designed to provide water at a suitable temperature, as well as soap and sanitizing agents, air driers, or single-service towels. Adequate facilities for showering and/or changing clothes should be provided, when appropriate.

### 3.3.8 ALLERGEN CROSS-CONTAMINATION REDUCTION CONTROL

Adequate precautions must be taken to reduce the potential for allergen cross-contact of raw materials, other ingredients, in-process materials, dietary ingredients, and contact surfaces with 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 using one or more of the following means: location, time, partition, air-flow systems, dust-control systems, enclosed systems, or other effective means.

### 3.3.9 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.

## 3.4 Equipment, Instruments, and Utensils

Equipment, instruments, and utensils used in the manufacture of dietary ingredients must be of appropriate design, construction, and workmanship to enable them to be suitable for their intended use, to be and suitably located to facilitate operations for their intended use, and to be adequately cleaned and properly maintained to protect against allergen cross-contact and contamination.

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.

Major equipment and permanently installed processing lines used during the production, packaging, and labeling of dietary ingredients 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.

Equipment that is in areas where food is manufactured, processed, packed, or held and that does not come into contact with food must be so constructed that it can be kept in a clean and sanitary condition.

Holding, conveying, and manufacturing systems, including gravimetric, pneumatic, closed, and automated systems, must be of a design and construction that enables them to be maintained in an appropriate clean and sanitary condition.

### 3.4.1 DESIGN AND CONSTRUCTION

Equipment and utensils must be appropriate in design and construction and used appropriately to do the following:

- Prevent contamination of dietary ingredient 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 dietary ingredients
- Withstand the environment in which they are used in manufacturing, cleaning, and sanitizing
- Have seams that are smoothly bonded or maintained to minimize accumulation of dirt, filth, organic material, particles of dietary ingredient, or any other extraneous materials or contaminants, and thus minimize the opportunity for growth of microorganisms and allergen cross-contact
- Constructed so that surfaces that contact dietary ingredients are not corrosive, reactive, additive, or absorptive so as to alter the quality of the dietary ingredient beyond the established requirements
- Must be maintained to protect dietary ingredients from allergen cross-contact and from being contaminated by any source

Automated, mechanical, or electronic equipment that is used to manufacture, package, label, or hold a dietary ingredient must be designed or selected to ensure that the dietary ingredient 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.

### 3.4.2 INSTALLATION AND MAINTENANCE

Equipment and utensils must be installed and/or maintained to facilitate cleaning the equipment and utensils and adjacent spaces and to protect dietary ingredients from being contaminated by any source. Equipment and utensils must be maintained in an adequate condition through appropriate cleaning and sanitizing, as necessary. Insofar as necessary, equipment must be taken apart for thorough cleaning.

Each freezer, refrigerator, and cold storage compartment used to store and hold dietary ingredients must do the following:

- Be fitted with an 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
- 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 dietary ingredients or dietary ingredient-contact surfaces, or that are used to clean food-contact surfaces, must be treated in such a way (e.g., proper filtration) that food is not contaminated.

Instruments or controls used in the manufacturing, packaging, labeling, or holding of a dietary ingredient, 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, periodically calibrated, adequately maintained, and adequate in number for their designated uses.

### 3.4.3 OPERATION AND CALIBRATION

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

Instruments and controls used in manufacturing or testing raw materials, other ingredients, in-process material, or dietary ingredients must be calibrated before first use at a frequency specified in writing by the manufacturer of the instrument or control and at established 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 \(1251\)](#).

Automated, mechanical, or electronic equipment that is used to manufacture, package, label, or hold a dietary ingredient must be routinely calibrated, inspected, or checked to ensure proper performance. The quality unit must 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 QC unit.

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

Quality unit personnel must do the following:

- 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
- Review and approve controls to ensure that automated, mechanical, or electronic equipment functions in accordance with its intended use

### 3.4.4 CLEANING AND MAINTENANCE

Equipment, utensils, and any other contact surfaces used to manufacture, package, label, or hold raw materials, other ingredients, in-process materials, or dietary ingredients must be maintained, cleaned, and sanitized as necessary to protect against allergen cross-contact and contamination of raw materials, other ingredients, in-process materials, and dietary ingredients. 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 the cleaning of equipment and its subsequent release for use in the manufacture of dietary ingredients. Cleaning procedures should contain enough details to enable operators to clean each type of equipment in a reproducible and effective manner. These procedures should include the following:

- Assignment of responsibility for cleaning of equipment
- Cleaning 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
- Establishment of 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 ingredients, 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 ingredient, the contact surfaces must be inspected and adequately cleaned and sanitized as necessary to prevent build-up 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 or in close proximity to the equipment.

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

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

Heat-treated pallets (or plastic pallets) must be used in areas where raw materials, other ingredients, in-process materials, dietary ingredients, 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 raw materials, other ingredients, in-process materials or dietary ingredients must be in a clean, dry, and 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 raw materials, other ingredients, in-process materials, or dietary ingredients. 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 ingredient, the contact surfaces must be adequately cleaned and sanitized, as necessary.

Single-service articles (e.g., 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 raw materials, other ingredients, in-process materials, dietary ingredients, 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.

### 3.4.5 EQUIPMENT AND INSTRUMENT QUALIFICATION

"Fitness for purpose" must be demonstrated for equipment and instruments. There are many ways of demonstrating that equipment and instruments meet fitness for purpose and are 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 on 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 ingredient industry to manufacture, package, label, test, and hold dietary ingredients. A 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, it 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.

### 3.4.6 COMPUTERIZED SYSTEMS

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

Appropriate IQ and OQ should demonstrate the suitability of the computer hardware and software to perform assigned tasks.

cGMP-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.

When critical data are being entered manually, an additional check on the accuracy of the entry must be done, either 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 changes, 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 cGMP-related computerized systems. Data can be recorded by a second means in addition to the computer system. Test records should not be written to erasable media not covered by an audit trail, such as thumb drives.

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

**3.4.6.1 Computer systems procedures and controls:** cGMP-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, such as the system being turned off and data not being 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, and 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

**3.4.6.2 Electronic signatures:** Signed electronic records must contain information associated with the signing that clearly indicates the following: the printed name of the signer, the date and time when the signature was executed, and the meaning (e.g., 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. Individuals responsible for electronic signatures must have a specific identification code and password. Persons who used electronic signatures must employ controls to ensure their security and integrity.

### 3.5 Physical Plant and Equipment Documentation

The following documentation must be made and kept for fulfilling the requirements of the physical plant and equipment quality system (see 1. *General Provisions*).

#### 3.5.1 WRITTEN PROCEDURES

Written procedures must be established and followed for the following:

- 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 raw materials, other ingredients, in-process materials, and dietary ingredients
- 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 raw material, other ingredient, in-process material, or dietary ingredient
- Calibrating, inspecting, and checking automated, mechanical, and electronic equipment and instruments
- Operating and maintaining cGMP-related computerized systems

#### 3.5.2 RECORDS

Records must be made and kept for the following:

- List of approved cleaning compounds, sanitizing agents, and corresponding safety data sheets
- Drawings for utility systems (e.g., water, steam, gases, compressed air, and heating, ventilation, and air conditioning)
- Physical plant and facility maintenance, cleaning, and sanitizing schedules, and logs of the date of maintenance and any cleaning and sanitizing unless such documentation is kept with the batch record
- Pest control
- Demonstrating that water, when used as a component of a dietary ingredient, meets all federal, state, and local standards of potability. Some intended uses of water in dietary ingredients may require the use of compendial grade [Purified water](#)
- 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 and each time the calibration is performed for instruments and controls used in manufacturing or testing a raw material, other ingredient, in-process material, or dietary ingredient
  - The documentation must identify the instrument or control calibrated and date of its 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
- Back-up file(s) of current and outdated software, as necessary, for retrieval of records that are required to be kept, and of data entered into the computer system used to manufacture, package, label, and hold dietary ingredients

Back-up 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.

#### 4. MATERIALS MANAGEMENT OPERATIONS AND CONTROLS

The person(s) authorized to release raw materials, other ingredients, packaging materials, labeling, and dietary ingredients should be specified. No materials should be released or used before the satisfactory completion of evaluation by the quality unit(s) unless appropriate systems are in place to allow for such use (e.g., release under quarantine, see 4.5 *Holding, Distribution, and Transportation*).

##### 4.1 Establishing Material and In-Process Production Specifications

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

###### 4.1.1 RAW MATERIAL AND OTHER INGREDIENT SPECIFICATIONS

Specifications must be established for each raw material and other ingredient that is used in the manufacture of a dietary ingredient to ensure that the specifications for its purity, strength, and composition are met. The specification for the raw materials and other ingredients should include test specifications for the following:

- Identity (i.e., identification)
- 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 ingredients
- Applicable specific tests (e.g., peroxide value, anisidine value for oil rancidity)
- Manufacturing processing quality tests (e.g., particle size, bulk density)

Starting materials and processing aids used to manufacture dietary ingredients should be of suitable quality to ensure that the finished dietary ingredient meets appropriate standards of identity, strength, purity, composition, and limits on contaminants.

Other ingredients used in manufacturing dietary ingredient preparations should meet *USP*, *NF*, or *Food Chemical Codex* standards. When such standards do not exist, other ingredients may be used in dietary ingredients if they have been shown to be of acceptable food grade quality using other suitable procedures.

Raw materials and other ingredients either must not contain levels of microorganisms that may render the food injurious to the health of humans, or must be pasteurized or otherwise treated during manufacturing operations so that they no longer contain levels that would cause the dietary ingredient to be adulterated.

Other ingredients may be added to dietary ingredients provided that the other ingredients comply with applicable regulatory requirements and do not interfere with the assay and tests prescribed for determining compliance with the dietary ingredient compendial specification.

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

Each raw material and other ingredient received from a supplier that is liable to contamination with microorganisms, filth, insect infestation, allergens, aflatoxins, other natural toxins, pesticides, organic impurities (e.g., residual solvents), inorganic impurities (e.g., elemental impurities), 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. The following *USP* chapters should be consulted:

- [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 \(2232\)](#).

Raw materials and other ingredients susceptible to contamination with aflatoxin or other natural toxins must comply with FDA regulations for poisonous or deleterious substances before these raw materials or other ingredients are incorporated into the dietary ingredient and ultimately finished food.

Raw materials, other ingredients, and rework susceptible to contamination with pests, undesirable microorganisms, or extraneous material must comply with applicable FDA regulations for natural or unavoidable defects if a manufacturer wishes to use the materials in manufacturing food.

#### 4.1.2 IN-PROCESS PRODUCTION SPECIFICATIONS

Specifications must be established for in-process production for any point, step, or stage in the master production and control record in which control is necessary to help ensure that the specifications are met for the identity, purity, strength, and composition of the dietary ingredients 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 ingredient.

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

#### 4.1.3 LABELING AND PACKAGING MATERIAL SPECIFICATIONS

Specifications must be established for labeling (see [Labeling \(7\)](#)) and packaging materials that come in contact with dietary ingredients (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 \(670\)](#), [Containers—Performance Testing \(671\)](#)). Packaging that may come into contact with dietary ingredients 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 ingredient.

#### 4.1.4 IN-PROCESS DIETARY INGREDIENT SPECIFICATIONS

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

- Identity (i.e., identification) should be established through a validated method that has a high degree of specificity to differentiate between similar dietary ingredients
- 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 ingredients
- Applicable specific tests (e.g., peroxide value, anisidine value for oil rancidity)
- Applicable performance tests (e.g., particle size)
- Applicable manufacturing quality tests (e.g., content uniformity)

Dietary ingredients that have a *USP* monograph should comply with the monograph standard and other applicable standards in that compendium.

**4.1.4.1 Defect action levels:** Some dietary ingredients, even when produced under cGMPs, contain naturally occurring unavoidable defects that at low levels present no health hazard. The FDA set defect action levels because it is economically impractical to grow, harvest, or process raw products that are totally free of non-hazardous, naturally, and 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 ingredient 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 ingredient containing defects at levels that render that dietary ingredient adulterated with another lot of dietary ingredient is not permitted and renders the final dietary ingredient adulterated, regardless of the defect action level of the final dietary ingredient.

#### 4.1.5 RECEIVED IN-PROCESS DIETARY INGREDIENT SPECIFICATIONS

Specifications must be established for an in-process dietary ingredient received from a supplier for packaging and labeling and for its distribution rather than for return to the supplier. The specification must provide sufficient assurance that the in-process dietary ingredient received is adequately identified and consistent with the purchase order or supplier quality agreement.

#### 4.1.6 FINISHED DIETARY INGREDIENT SPECIFICATIONS

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

### 4.2 Determining Compliance with Specifications

#### 4.2.1 GENERAL

Quality unit personnel must determine whether the specifications set for raw materials, other ingredients, in-process materials, packaging materials, labeling, in-process dietary ingredients, received in-process dietary ingredients, and finished dietary ingredients are met.

QC (laboratory control) unit personnel must conduct the necessary tests to determine whether the specifications for raw materials, other ingredients, in-process materials, and dietary ingredients comply with specifications. On the basis of adequate process verification, in-process controls, and statistical confidence, a reduced testing (or sampling) plan can be used as an alternative to fully testing of contaminants in every batch of material.

Tests and examinations that are used to determine whether material specifications are met must be appropriate for their intended use, and scientifically validated methods according to [Validation of Compendial Procedures \(1225\)](#).

The QC unit must conduct or review and approve an OOS investigation prior to making a material use and disposition decision on any dietary ingredients. Corrective action plans must be developed and implemented when a dietary ingredient is confirmed to be out-of-specification and a root cause has been identified.

#### 4.2.2 RAW MATERIALS AND OTHER INGREDIENTS

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

- Conduct appropriate tests or examinations for all of the test specifications
- Rely on the certificate of analysis from the supplier of the raw material and other ingredient received, provided the following:
  - The supplier is qualified by establishing the reliability of the supplier's certificate of analysis through confirmation of the results of the supplier's tests or examinations, 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 (i.e., requalified)
  - Quality unit personnel have reviewed and approved the documentation setting forth the basis for qualification and requalification of the supplier

#### 4.2.3 IN-PROCESS PRODUCTION

In-process points, steps, or stages where control is necessary to ensure the quality of the finished batch of dietary ingredients 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 ingredient to meet specifications.

#### 4.2.4 DIETARY INGREDIENTS

For every batch of dietary ingredients, the manufacturer must verify that the batch meets product specifications for identity, purity, strength, and composition. Reduced testing (i.e., reduced sampling) of contaminants that may adulterate or may lead to adulteration of the dietary ingredient can be applied to batches that have been identified through a sound statistical sampling plan:

- Established specifications for limits on those types of contamination that may adulterate or that may lead to adulteration of the dietary ingredient would verify that the production process control system is producing a dietary ingredient that meets product specifications
- Appropriate tests or examinations must be conducted to determine compliance with the applicable specifications
- Adequate documentation must be provided of the basis for determining how compliance with reduced testing of contaminants will ensure that the finished batch of dietary ingredients will meet all product specifications for the limits on those types of contamination that may adulterate or that may lead to adulteration of the dietary ingredient
- Quality unit personnel must review and approve all supporting documentation for reduced testing

#### 4.2.5 RECEIVED IN-PROCESS DIETARY INGREDIENT

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

#### 4.2.6 PACKAGING MATERIAL AND LABELING

Before packaging material is used, 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, at a minimum.

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.

#### 4.2.7 FINISHED DIETARY INGREDIENTS

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

#### 4.2.8 DISPOSITION DECISION FOR MATERIALS

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

For raw materials, other ingredients, in-process materials, packaging materials, labeling, and dietary ingredients 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 ingredient, and that the dietary ingredient is packaged and labeled as specified in the master packaging record.

For raw materials and other ingredients that do not meet specification(s) for identity (i.e., identification), QC personnel must reject the raw material or other ingredient, which must not be used in manufacturing the dietary ingredient.

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

The quality unit personnel must not approve and release for distribution any batch or reprocessed batch of dietary ingredient in the following situations:

- When any component in the batch does not meet its identity specification
- When all product specifications are not met
- When a dietary ingredient has not been manufactured, packaged, labeled, and held under conditions to prevent adulteration
- When a dietary ingredient was received from a supplier for packaging or labeling as a dietary ingredient and for distribution rather than return to the supplier, but without sufficient assurance provided to adequately identify the product and to determine that the product is consistent with its purchase order

#### 4.2.9 TREATMENTS, IN-PROCESS ADJUSTMENTS, AND REPROCESSING

A rejected dietary ingredient must not be reprocessed, and a rejected 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 ingredient, unless the following is done:

- 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 ingredient and that the dietary ingredient is packaged and labeled as specified in the master production and control record
- All raw materials and other ingredients in the batch met its identity (i.e., identification) specification

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

Any batch of dietary ingredient that is reprocessed, that contains raw materials and other ingredients 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 ingredient must be approved by quality unit personnel before release for distribution.

Prior to approving any batch of dietary ingredient for reprocessing or an in-process adjustment, the quality unit should determine what tests should be performed to verify the effectiveness of the reprocessing/in-process adjustment to ensure that specifications have not been compromised.

Quality unit personnel must not approve and release for distribution any batch or reprocessed batch of dietary ingredient in the following situations:

- When any component in the batch does not meet its identity specification
- When all product specifications have not been met
- When the dietary ingredient has not been manufactured, packaged, labeled, and held under conditions to prevent adulteration
- When the dietary ingredient was received from a supplier for packaging or labeling as a dietary ingredient and for distribution rather than return to the supplier, but without sufficient assurance provided to adequately identify the product and to determine that the product is consistent with its purchase order

### 4.3 Receiving and Release of Materials

#### 4.3.1 RAW MATERIALS, OTHER INGREDIENTS, PACKAGING MATERIALS, AND LABELS

The person responsible for receiving raw materials, other ingredients, packaging materials, or labels must visually examine each immediate container or grouping of immediate containers in a shipment that is received for the appropriate content label, container damage, or broken seals to determine whether the container condition may have resulted in contamination or deterioration of the raw materials, other ingredients, packaging materials, or labels. The person must visually examine the supplier's invoice, guarantee, or certification in a shipment that is received to ensure the raw materials, other ingredients, packaging materials, and labels are consistent with the purchase order.

Raw materials received via bulk truck or railcar must include verification that the vehicle is dedicated to that service or that the vehicle has been properly cleaned and the prior load does not pose a risk of contamination.

Raw materials and other ingredients must be inspected and segregated or otherwise handled as necessary to ascertain that they are clean and suitable for processing into a dietary ingredient and must be stored under conditions that will protect against allergen cross-contact, against contamination, and minimize deterioration. Raw materials must be washed or cleaned as necessary to remove soil or other contamination. Water used for washing, rinsing, or conveying food must be safe and of adequate sanitary quality (i.e., potable water).

The raw materials, other ingredients, packaging materials, and labels must be placed in quarantine before they are used in the manufacture of a dietary ingredient until the following occurs:

- Representative samples of each unique shipment of raw materials, other ingredients, packaging materials, and labels received are collected, as well as of each unique lot within each unique shipment of raw materials, other ingredients, packaging materials, and labels
- Quality unit personnel review and approve the results of any tests or examinations conducted on raw materials, other ingredients, packaging materials, and labels
- Quality unit personnel approve and release from quarantine the raw materials, other ingredients, packaging materials, and labels for use in the manufacture of a dietary ingredient, including approval of any treatment or in-process adjustments of raw materials, other ingredients, packaging materials, and labels to make them suitable for use in the manufacture of a dietary ingredient

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

Raw materials, other ingredients, packaging materials, and labels must be held under conditions that will protect against contamination and deterioration and avoid mix ups.

#### 4.3.2 PRODUCT RECEIVED FOR PACKAGING AND LABELING AS A DIETARY INGREDIENT

The person responsible for receiving product for packaging and labeling as a dietary ingredient and for distribution rather than for return to the supplier must visually examine each immediate container or grouping of immediate containers in a shipment for appropriate content label, container damage, or broken seals to determine whether the container condition may have resulted in contamination or deterioration of the received product. That 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 ingredient until the following occurs:

- Representative samples of each unique shipment of received product and of each unique lot within each unique shipment of received product are collected
- 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 it meets specifications
- Quality unit personnel approve the received product for packaging and labeling as a dietary ingredient and release 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 by 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), as well as to the dietary ingredient 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.

### 4.4 Representative Samples and Reserve Samples

#### 4.4.1 REPRESENTATIVE SAMPLES

Quality unit personnel must collect representative samples of the following:

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

The representative samples of dietary ingredients must be held in a suitable container–closure system that represents similar barrier properties to the container–closure system in which the dietary ingredient is ultimately sold to the user.

A sampling room or booth must be used to sample raw materials and other ingredients to protect material from allergen cross-contact and 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 on appropriate criteria such as component variability, statistical confidence levels, 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 the following:

- Containers should be cleaned prior to opening
- Containers should be opened, sampled, and resealed in a manner designed to prevent contamination of their contents and contamination of other raw materials, other ingredients, product containers, or closures
- 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 [\(561\)](#).

#### 4.4.2 RESERVE SAMPLES

Quality unit personnel must collect and hold reserve samples of each lot of packaged and labeled dietary ingredients that is distributed, 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.

Reserve samples of dietary ingredients must be identified with the batch, lot, or control number. The reserve sample of each batch of dietary ingredients must consist of at least twice the quantity necessary for all tests or examinations to determine whether the dietary ingredient meets product specifications and must be collected and retained for at least 1 year past its retest or expiry date.

### 4.5 Holding, Distribution, and Transportation

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

#### 4.5.1 HOLDING

Raw materials and other ingredients and dietary ingredients must be held under appropriate conditions of temperature, humidity, and light so that the identity, purity, strength, and composition of the raw materials and other ingredients and dietary ingredients are not affected. Raw materials and other ingredients, along with rework, must be held in bulk, or in containers designed and constructed so as to protect against contamination and must be held at such temperature and relative humidity and in such a manner as to prevent the food from becoming contaminated. Frozen raw materials and other ingredients must be kept frozen. If thawing is required prior to use, it must be done in a manner that prevents the raw materials and other ingredients from becoming contaminated. Liquid or dry raw materials and other ingredients received and stored in bulk form must be held in a manner that protects against allergen cross-contact and against contamination. Raw materials and other ingredients that are food allergens and rework that contains food allergens must be identified and held in a manner that prevents allergen cross-contact.

Storage of dietary ingredients must be under conditions that will protect against contamination, as well as the deterioration of the dietary ingredient and the container.

Packaging materials and labeling must be held under appropriate conditions so that they are not adversely affected. Raw materials, other ingredients, dietary ingredients, packaging materials, and labeling must be held under conditions that do not lead to the mix-up or contamination of raw materials, other ingredients, dietary ingredients, 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.

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

Reserve samples of dietary ingredients must be held in a suitable container–closure system that represents similar barrier properties to the container–closure system in which the dietary ingredient is ultimately sold to the user.

Reserve samples of dietary ingredients must be held in a manner that protects against contamination and deterioration. Reserve samples of dietary ingredients must be held under conditions consistent with the label conditions stated on the product labels. If no storage conditions are recommended on the label (e.g., for in-process dietary ingredients), they must be held under ordinary storage conditions consistent with expected storage conditions for the finished product. Reserve samples of dietary ingredients must be held using the same container–closure system in which packaged and labeled dietary ingredients are distributed. If distributing dietary ingredients that are to be packaged and labeled, a container–closure system that provides essentially the same characteristics to protect against contamination or deterioration must be used.

Reserve samples must be retained for 1 year past the retest or expiry date of the dietary ingredient for use in appropriate investigations.

#### 4.5.2 REJECTED MATERIALS

Any raw material, other ingredients, packaging material, labels, and products received for packaging and labeling as a dietary ingredient 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 any electronic controls.

#### 4.5.3 RETURNED DIETARY INGREDIENTS

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

Returned dietary ingredients must be destroyed or otherwise suitably disposed of unless the outcome of a material review and disposition decision is that QC personnel do one of the following:

- Approve the salvage of the returned dietary ingredient for redistribution
- Approve the returned dietary ingredient for reprocessing

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

Any returned dietary ingredients that are reprocessed must meet all dietary ingredient specifications, and QC personnel must approve or reject the release for distribution any returned dietary ingredient that is reprocessed.

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

#### 4.5.4 DISTRIBUTION

Dietary ingredients must be distributed under conditions that will protect the dietary ingredient against contamination and deterioration. The first manufactured batch of a dietary ingredient should be distributed first. Distributing operations must be designed to facilitate recall of dietary ingredients, if necessary.

#### 4.5.5 TRANSPORTATION OPERATIONS

All transportation operations must be conducted under such conditions and controls necessary to prevent dietary ingredients from becoming adulterated and to protect against deterioration of the dietary ingredient and the container during transportation.

Vehicles and transportation equipment used in transportation operations must meet the following standards:

- Adequately designed and maintained in a sanitary condition for their intended use to prevent raw materials and other ingredients and dietary ingredients from becoming adulterated during transportation operations
- Designed, maintained, and equipped as necessary to provide adequate temperature control to prevent raw materials and other ingredients and dietary ingredients requiring temperature control from becoming adulterated during transportation
- Stored in a manner that prevents it from harboring pests or becoming contaminated in any other manner that could result in raw materials and other ingredients or dietary ingredients 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 raw materials and other ingredients and dietary ingredients from becoming unsafe during transportation. Such operations include taking the following effective measures:

- Segregation, isolation, or the use of packaging to protect raw materials and other ingredients and dietary ingredients from contamination from other articles in the same load
- Ensure that raw materials and other ingredients and dietary ingredients that require temperature control for safety and quality are transported under adequate temperature control
- Restrict the co-shipment with a non-food item, which might render the raw materials and dietary ingredients to become 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.

Considering specifications provided by the shipper when appropriate, loaders must determine if the vehicle or transportation equipment is in appropriate sanitary and operational condition for the transport of raw materials and other ingredients and dietary ingredients.

Upon receipt of raw materials and other ingredients and dietary ingredients, receivers must take steps to adequately assess whether the raw materials and other ingredients and dietary ingredients 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 raw materials and other ingredients and dietary ingredients 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.

### 4.6 Materials Management Operations and Control Documentation

The following documentation must be made and kept for fulfilling the requirements of the material management controls quality system (see 1. General Provisions).

#### 4.6.1 WRITTEN PROCEDURES

Written procedures must be established and followed for the following:

- Preparing, reviewing, and approving material and in-process production specifications
- Supply chain control program
- 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 supply-chain control program
- Holding and distributing operations
- Receiving and conducting material reviews and making disposition decisions for returned dietary ingredients

#### 4.6.2 RECORDS

Records must be made and kept for the following:

- Specifications for raw materials, other ingredients, in-process production, packaging materials, labeling, in-process dietary ingredients, received in-process dietary ingredients, and finished dietary ingredients
- List of approved suppliers of raw materials, other ingredients, packaging materials and labeling, and corresponding supplier qualification evaluation reports for the purpose of relying on the supplier's certificate of analysis
- Documentation explaining why meeting in-process specifications, in combination with meeting component specifications, help to ensure that the dietary ingredient meets the specifications for identity, purity, strength, and composition, as well as for limits on those types of contamination that may adulterate or may lead to adulteration of the finished batch of the dietary ingredient
- Documentation explaining why the results of appropriate reduced tests or examinations for dietary ingredients ensure that the dietary ingredient meets all product specifications
- Receiving records (e.g., certificates of analysis, supplier's invoice, and supplier's guarantee) for materials
- Inventory control records documenting material history of use
- Documentation at the time of performance that demonstrates that QC 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 ingredient distribution
- Documentation of any material review and disposition decisions on a returned dietary ingredient
- The results of any testing or examination of returned dietary ingredients to determine compliance with product specifications
- Documentation of the re-evaluation by quality unit personnel of any dietary ingredient that is reprocessed and the determination by quality unit personnel of whether the reprocessed dietary ingredient meets in-process dietary ingredient specifications

### 5. PRODUCTION OPERATIONS AND CONTROLS

All dietary ingredient manufacturing, processing, packing, and holding must be conducted under such conditions and controls that are necessary to minimize the potential for the growth of microorganisms, allergen cross-contact, contamination of food, and deterioration of dietary ingredient. Equipment, containers, and utensils used to convey, hold, or store raw materials, other ingredients, work-in-process, rework, or dietary ingredients must be constructed, handled, and maintained during manufacturing, processing, packing, and holding in a manner that protects against allergen cross-contact and contamination.

#### 5.1 Master Production Records

Written master production records must be prepared and followed for each unique formulation of dietary ingredients manufactured, and for each batch size to ensure batch-to-batch uniformity in the finished dietary ingredient. The master production record for each in-process material (i.e., intermediate) and dietary ingredient should be prepared, dated, and signed by one person in production, and then independently checked, dated, and signed by a person in the quality unit.

The master production record may include all manufacturing, packaging, and labeling directions and controls, or it may be separated into two records: one for manufacturing and another for packaging and labeling.

The master production record must do the following:

- 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 ingredient and that the dietary ingredient is packaged and labeled as specified in the master production and control record
- Establish controls and procedures to ensure that each batch of dietary ingredient that is manufactured meets in-process specifications

The master production record must include the following:

- The name of the intermediate (i.e., in-process material) or dietary ingredient to be manufactured and an identifying document reference code
- The strength, concentration, weight, or measure of each raw material and other ingredient for each batch size
- A complete list of raw materials and other ingredients to be used, designated by names and codes specific to identify any special quality characteristics
- An accurate statement of the weight or measure of each raw material and other ingredient to be used
  - When the quantity is not fixed, the calculation for each batch size or rate of production should be included
  - Variations to quantities should be included where they are justified

- The identity and weight or measure of each other ingredient and dietary ingredient that will be declared on the finished dietary ingredient (preparation) list of ingredients
- Detailed production instructions, including the following:
  - Sequences to be followed
  - Ranges of process parameters to be used
  - Sampling instructions and in-process controls with their acceptance criteria, when appropriate
  - Time limits for completion of individual processing steps and/or the total process, when appropriate
  - Expected yield ranges at appropriate phases of processing or time
- A statement of theoretical yield of a manufactured intermediate or dietary ingredient (preparation) expected at each point, step, or stage of the manufacturing process where control is needed to ensure the quality of the dietary ingredient, and of the expected yield at the end of manufacturing the dietary ingredient, including the maximum and minimum percentages of theoretical yield beyond which a deviation investigation of a batch is necessary and a material review is conducted and disposition is made
- Where appropriate, special notations and precautions to be followed, or cross-references to them
- The instructions for storage of the intermediate or finished dietary ingredient to assure its suitability for use, including a description of packaging materials and a representative label, or cross-reference to the physical location of the actual or representative label, and special storage conditions with time limits, when appropriate

The master production 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 ingredient and that the dietary ingredient is packaged and labeled as specified in the master production and control 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 ingredient and that the dietary ingredient is packaged and labeled as specified in the master production and control record
  - Such specific actions must include verifying the weight or measure of any raw material and other ingredient and verifying the addition of any raw material and other ingredient
  - For manual operations, such specific actions must include the following:
    - One person weighing or measuring a raw material and other ingredient and another person verifying the weight or measure
    - One person adding the raw material and other ingredient and another person verifying the addition
- Special notations and precautions to be followed
- Corrective action plans for use when a specification is not met

## 5.2 Executed Batch Production Records

An executed batch production record (paper or electronic) must be prepared or generated every time a batch of dietary ingredients is manufactured, and it must include complete information relating to the production and control of each batch. The executed batch production and control record must accurately follow the appropriate master production and control record, and each step in the production of the batch must be performed.

The executed batch production record must include the following:

- The batch, lot, or control number of the dietary ingredient, of each lot of packaged and labeled dietary ingredient from a finished batch of dietary ingredient, and of each lot of dietary ingredient from the finished batch of dietary ingredient that is distributed to another person for packaging or labeling
- The identity of equipment and processing lines used in producing the batch (exceptions can be noted when equipment is dedicated or the identity of the product or processing is self-evident)
- 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 raw material and other ingredient used or, when applicable, to a used product that was received from a supplier for packaging and labeling as a dietary ingredient, packaging, and labeling
- The identity and weight or measure of each raw material and other ingredient 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 ingredient meets the in-process dietary ingredient and finished dietary ingredient specifications

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

- The date on which each step of the master production and control record was performed
- The initials of the person performing each step, including initials of the persons responsible for the following:
  - Weighing or measuring each raw material and other ingredient used in the batch

- Verifying the weight or measure of each raw material and other ingredient used in the batch
- Adding the raw material and other ingredient to the batch
- Verifying the addition of raw materials and other ingredients to the batch
- Documentation at the time of performance of packaging and labeling operations, including the following:
  - 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
  - The results of any tests or examinations conducted on a packaged and labeled dietary ingredient, including repackaged or relabeled dietary ingredients, or a cross-reference to the physical location of such results
- Documentation at the time of performance that quality unit personnel did the following:
  - Reviewed the batch production record, including reviewing any monitoring operation required for determining compliance to material specifications and reviewing the results of any tests and examinations, including tests and examinations conducted on raw materials, other ingredients, in-process materials, finished batches of dietary ingredients, and packaged and labeled dietary ingredients
  - 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 ingredient, including a repackaged or relabeled dietary ingredient
- Documentation at the time of performance of any required material review and disposition decision
- Documentation at the time of performance of any reprocessing

### 5.3 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 ingredient 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 ingredient to prevent contamination of raw materials and other ingredients or dietary ingredients. These precautions include the following:

- Performing manufacturing operations under conditions and controls that protect against the potential for growth of microorganisms and the potential for allergen cross-contact and contamination
- Protecting dietary ingredients from contaminants that may drip, drain, or be drawn into the dietary ingredient
- Washing and cleaning raw materials and other ingredients 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 ingredient when the water may be used as a raw material or may become another ingredient of the finished batch of dietary ingredient
- Performing chemical, microbiological, or other testing as necessary to prevent the use of contaminated raw materials and other ingredients
- Sterilizing, pasteurizing, freezing, refrigerating, controlling hydrogen-ion concentration (pH), controlling humidity, controlling water activity (aw), or using any other effective means to remove, destroy, or prevent the growth of microorganisms and prevent decomposition
- Washing, cutting, sorting and inspecting, mashing, dewatering, cooling, shredding, extruding, and drying performed in a manner that protects dietary ingredients against allergen cross-contact and against contamination
- Heat blanching when required in the preparation of dietary ingredients capable of supporting microbial growth, effected by heating the food to the required temperature, holding it at this temperature for the required time, and then either rapidly cooling the food or passing it to subsequent manufacturing without delay
  - Growth and contamination by thermophilic microorganisms in blanchers must be minimized by the use of adequate operating temperatures and by periodic cleaning and sanitizing, as necessary
- Treating or maintaining solutions and other similar preparations held and used repeatedly over time in such a manner that they are protected against allergen cross-contact and against contamination, and minimizing the potential for the growth of undesirable microorganisms
- Holding food at risk for the rapid growth of microorganisms of public health significance in a manner that prevents the food from becoming adulterated, such as keeping it at acceptable temperatures
- Processing and maintaining food that relies principally on the control of water activity for preventing the growth of undesirable microorganisms at a safe moisture level
- Monitoring and maintaining food that relies principally on the control of pH for preventing the growth of undesirable microorganisms at or below a pH of 4.6
- Identifying and holding any raw materials and other ingredients or dietary ingredients for which a material review and disposition decision is required and doing so in a manner that protects raw materials and other ingredients or dietary ingredients not under a

material review against contamination and mix-ups with those that are under a material review

- Performing mechanical manufacturing steps (e.g., washing, peeling, trimming, cutting, sorting, inspecting, mashing, shredding, drying, grinding, blending, and sifting) by any effective means to protect the dietary ingredients against contamination, such as the following examples:
  - Cleaning and sanitizing contact surfaces
  - Using temperature controls
  - Using time controls
- Using effective measures to protect against the inclusion of metal or other foreign material in raw materials and other ingredients or dietary ingredients, such as filters or strainers, traps, magnets, or electronic metal detectors
- Segregating and identifying all containers for a specific batch of dietary ingredients to identify their contents and, when necessary, the phase of manufacturing
- Identifying all processing lines and major equipment used during manufacturing to indicate their contents, including the name of the dietary ingredient and the specific batch or lot number and, when necessary, the phase of manufacturing
- Protecting dietary ingredients transported by conveyor against allergen cross-contact and against contamination as necessary

#### 5.4 Quality Unit Responsibilities for Production

Quality unit personnel must do the following:

- Review and approve all master production and control records and all modifications to them
- Review and approve all master packaging and labeling records (if separate from master production and control records) 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 ingredients conforms to its specifications
- Make a disposition decision (i.e., approving and releasing, or rejecting) each finished batch of dietary ingredients, including any reprocessed finished batch of dietary ingredients, for distribution

#### 5.5 Disposition Decision for Production

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

The quality unit personnel must not approve and release for distribution any batch or reprocessed batch of dietary ingredient in the following situations:

- Any raw material and other ingredient in the batch does not meet its identity specification
- It does not meet all product specifications
- It has not been manufactured, packaged, labeled, and held under conditions to prevent adulteration
- It was received from a supplier for packaging or labeling as a dietary ingredient and for distribution rather than return to the supplier, but without sufficient assurance to adequately identify the product and to determine that the product is consistent with its purchase order

For dietary ingredients, raw materials, and other ingredients that are adulterated, one of the following must be done:

- Disposed of in a manner that protects against the contamination of other ingredients
- If the adulterated dietary ingredients, raw materials, and other ingredients are capable of being reconditioned, one of the following must be done:
  - Recondition (if appropriate) using a method that has been proven to be effective; or
  - Recondition (if appropriate) and re-examine to find if it is not adulterated before being incorporated into other ingredients

#### 5.6 Production Operations and Controls Documentation

The following documentation must be made and kept for fulfilling the requirements of the production operations and controls quality system (see 1. *General Provisions*).

##### 5.6.1 WRITTEN PROCEDURES

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

- Preparation and approval of master production and control records
- Cleaning and inspecting manufacturing facilities
- Manufacturing production operations
- Quality unit responsibilities and operations

## 5.6.2 RECORDS

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

- Executed batch production and control records
- Equipment and production suite cleaning record
- Quality unit operations

## 6. PACKAGING AND LABELING OPERATIONS AND CONTROLS

### 6.1 General

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

Written procedures should describe 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. Food-packaging materials must be safe and suitable. 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 that show receipt, examination, or testing, as well as whether the shipment accepted or rejected.

### 6.2 Packaging Materials

#### 6.2.1 GENERAL PROCEDURES

Necessary actions must be taken to determine whether packaging for dietary ingredients meets specifications so that the condition of the packaging will ensure the quality of the dietary ingredients. Containers must provide adequate protection against any deterioration or contamination of the dietary ingredient that may occur during transportation and recommended storage. Food containers must be maintained in an adequate condition through appropriate cleaning and sanitizing, as necessary.

General chapter [\(659\)](#) provides packaging definitions, auxiliary packaging information, and storage condition definitions relevant to the storage and distribution of dietary ingredients, and it 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 ingredient beyond specified limits.

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

#### 6.2.2 TAMPER-EVIDENT PACKAGING

Dietary ingredients should use tamper-evident packaging. A tamper-evident package is one that has an indicator or barrier to entry that, if breached or missing, can reasonably be expected to provide visible evidence to the customer (i.e., dietary supplement manufacturer) that tampering has occurred. To reduce the likelihood of substitution of a tamper-evident 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-evident 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-evident feature should be designed to remain intact when handled in a reasonable manner during holding, manufacture, and distribution.

### 6.3 Labeling

#### 6.3.1 GENERAL PROCEDURES

Labeling must comply with applicable federal and state labeling regulations for dietary ingredients.

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

- Class I (standardized): fortified or fabricated nutrients whose contents have been controlled in some fashion; must meet 100% of the quantitative label claim
- Class II (non-standardized): naturally occurring nutrients, whose constituents occur naturally in an ingredient and whose level is not controlled; must meet at least 80% of the quantitative label claim

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

Labeling must comply with applicable federal and state labeling regulations for dietary ingredients.

For botanicals, the common or usual name and/or the Latin binomial of the botanical species must be listed on the label. The current edition of the American Herbal Product Association's *Herbs of Commerce* 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.

Labeling for dietary ingredients 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 ingredient, and it 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 also must be located on the label.

### 6.3.2 RETEST OR EXPIRY DATE

Dietary ingredient labeling must state a retest date or expiry date that is indicative of the date after which the dietary ingredient can no longer meet applicable specifications of identity, strength, quality, and purity when stored under labeled conditions. The expiry date must be supported by suitable stability data.

A written procedure must be designed to ensure that the correct retest date or expiry date is printed on the finished dietary ingredient labeling.

## 6.4 Labeling Issuance and Control

Access to the label storage areas (i.e., label control room) must be limited to authorized personnel. Procedures should be implemented 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, as well as 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 and control record.

Labeling issuance must be designed to prevent mix-ups. Strict control must be exercised over the issuance of labeling for use in finished dietary ingredient 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 they 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 the preset limits based on historical operating data, such discrepancies should be investigated. Label reconciliation is not required for cut or rolled labels if a 100% examination for correct labels is performed by appropriate electronic or electromechanical equipment during or after completion of finishing operations.

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.

## 6.5 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 ingredient; that the dietary ingredient is protected against allergen cross-contact, contamination, and the growth of undesirable microorganisms; and that the dietary ingredient is packaged and labeled as specified in the master packaging record. This must be done using any effective means, including the following:

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

Written procedures must be established and 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 ingredients 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 ingredients 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 ingredients, consisting of at least twice the quantity necessary for finished dietary ingredient specification tests and examinations, must be collected and retained for at least 1 year past its retest or expiry date.

In-process dietary ingredients 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 ingredient 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 ingredient through distribution must be traceable.

## 6.6 Repackaging and Relabeling

Dietary ingredients 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 ingredients must be examined to determine whether the repackaged or relabeled dietary ingredients meet all established specifications. Quality unit personnel must approve or reject each batch of repackaged or relabeled dietary ingredients prior to its release for distribution. Repackaged or relabeled ingredients should retain the original retest or expiry date.

[Good Repackaging Practices \(1178\)](#) should be consulted.

## 6.7 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 quality system (see 1. *General Provisions*).

### 6.7.1 WRITTEN PROCEDURES

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

- 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
- Determination and issuance of finished dietary ingredient retest or expiry date to batch packaging and labeling control records

### 6.7.2 RECORDS

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

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

## 7. LABORATORY OPERATIONS AND CONTROLS

### 7.1 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 raw materials, other ingredients, packaging materials, labeling, in-process materials, and dietary ingredients meet specifications.

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

- Use of criteria for establishing appropriate specifications
- Use of sampling plans for obtaining representative samples of the following:
  - Raw materials, other ingredients, packing materials, and labels
  - In-process materials
  - Finished batches of dietary ingredients
  - Product that is received for packaging or labeling as a dietary ingredient and for distribution rather than for return to the supplier
  - Packaged and labeled dietary ingredients
- Use of criteria for selecting appropriate examination and testing methods

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

QC personnel must verify that the laboratory examination and testing methodologies are appropriate for their intended use. QC 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 QC unit personnel and reviewed and approved by the appropriate QA unit personnel. Specifications should be established in accordance with accepted standards and consistent with the manufacturing process.

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

## 7.2 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 ingredients. 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 Standard) may be used without testing if stored under conditions consistent with the supplier's recommendations.

When 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 it against a primary reference standard. Each batch of secondary reference standards should be periodically requalified in accordance with a written protocol.

## 7.3 Scientifically Validated Test Procedures

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

Chemical, microbial, or extraneous-material testing procedures must be used when necessary to identify sanitation failures or possible allergen cross-contact and food contamination.

### 7.3.1 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 information chapters should be consulted:

- [Biological Assay Validation \(1033\)](#)
- [Validation of Alternative Microbiological Methods \(1223\)](#)
- [Validation of Microbial Recovery from Pharmacopeial Articles \(1227\)](#)

### 7.3.2 VERIFICATION OF OFFICIAL TEST PROCEDURES

If the test procedure is in an official compendium, such as USP-NF or AOAC International's *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 and residue on ignition, or simple instrumental determinations, such as pH measurements.

## 7.4 Test Procedures

Test procedures must have clear and complete descriptions 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
- Procedures that include, as applicable:
  - System suitability
  - Preparation of solutions and reagents
  - Preparation of standards and samples
  - Instrumental parameters
  - 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.

## 7.5 Transfer of Analytical Test Procedures

Testing materials for compliance to specifications is critical in establishing the quality of the dietary ingredient. 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. [Transfer of Analytical Procedures \(1224\)](#), summarizes the types of transfers that may occur and outlines the potential raw materials and other ingredients of a transfer protocol, and it 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.

## 7.6 Reduced Testing

### 7.6.1 GENERAL PROCEDURES

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

Reduced testing for contaminants should be based on 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
- Ongoing monitoring of the process using recognized statistical process control (SPC) techniques

General control procedures should be established to monitor critical in-process manufacturing attributes that if not properly controlled, could cause a failure to meet identity, strength, purity, composition, or limits on contaminants. Special controls should be used to ensure content uniformity of blended, encapsulated, enrobed, or other specialized dietary ingredients.

The following terms are useful when describing reduced testing:

- "Lot-by-lot inspection" means full 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 the probability that a lot has been 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 cGMP competence so as to implement reduced sampling inspection
- "Product qualification" means assessment of product (i.e., raw material, other ingredient, in-process material, or dietary ingredient) quality to determine its suitability for reduced sampling inspection

### 7.6.2 REDUCED TESTING REQUIREMENTS

Reduced sampling inspection may be used only when both the supplier's cGMP quality systems and product (i.e., the raw material, other ingredient, in-process material, or dietary ingredient) are qualified. The dietary ingredient certificate of analysis should clearly disclose when reduced testing principles are applied.

- Requirements for supplier qualification are the following:
  - The supplier must have established, documented, and followed effective and applicable cGMP quality systems for managing quality that involves the active participation of personnel
  - An assessment of the supplier's cGMP quality systems must be performed
  - Ongoing assessment of the supplier's cGMP quality systems should be performed on a specified frequency
  - The supplier must not have experienced changes in its cGMP quality systems that adversely affect product quality
- Requirements for product (i.e., raw material, other ingredient, in-process material, or dietary ingredient) qualification are the following:
  - An assessment for product qualification should not be made prior to the assessment of the supplier's cGMP quality systems
  - The preceding 3 or more consecutive lots have been accepted, and results of resubmitted lots are not included

The following is an example of a typical reduced inspection and rotational testing approach that can be performed:

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

### 7.6.3 RECEIVED RAW MATERIALS, OTHER INGREDIENTS, IN-PROCESS MATERIALS, AND DIETARY INGREDIENTS

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 raw materials and other ingredients 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 raw material and other ingredient.

Each batch of raw material and other ingredient received from a supplier must be tested or examined against established specifications for contamination if it is liable to be contaminated with microorganisms, filth, insect infestation, allergens, aflatoxins, other natural toxins, pesticides, organic impurities (e.g., residual solvents), 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. In such cases, reduced testing of examination must not apply until risk is mitigated by the supplier.

### 7.6.4 IN-PROCESS MATERIALS AND DIETARY INGREDIENTS

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 ingredients provided that at least one representative measure (i.e., rotational testing) is performed.

## 7.7 Out-of-Specification (OOS) Investigations

Written procedures must be established and followed for investigating deviations or the failure of a batch of material to meet specifications (i.e., OOS 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.

## 7.8 Stability Testing

A documented on-going testing program must be designed to monitor the stability characteristics of dietary ingredients, and the results must be used to establish appropriate storage conditions and retest or expiry dates for the dietary ingredients. Test procedures used in stability testing must be validated and indicate stability. Stability samples should be stored in container–closure systems that simulate the packaging proposed to distribute the finished dietary ingredient in the marketplace. If multiple container–closure systems are used, stability and expiry date assignment can be satisfied by testing the container–closure system with the least desirable barrier properties. Stability studies should include testing of those attributes of the dietary ingredient that are susceptible to change during storage and that influence the quality of the dietary ingredient.

Ideally the first 3, but at minimum 1, production batches should be placed on the stability monitoring program to establish the product retest or expiry date. Thereafter, at least 1 batch per year of manufactured dietary ingredient (unless none are 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 =  $25 \pm 2^\circ$  and  $60\% \pm 5\%$  RH
- Intermediate =  $30 \pm 2^\circ$  and  $65\% \pm 5\%$  RH
- Accelerated =  $40 \pm 2^\circ$  and  $75\% \pm 5\%$  RH

Long-term studies also can be performed under the labeled storage conditions, such as at room temperature (ambient conditions) or in a cool, dry place ( $8^\circ$ – $15^\circ$  and not more than 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 ingredient. The following testing frequencies are recommended:

- Long term = 0, 3, 6, 9, 12, 18, 24, and 36 months
- Intermediate = 0, 3, 6, 9, and 12 months
- Accelerated = 0, 1, 2, 3, and 6 months

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

For ingredients intended for storage in a refrigerator, the storage conditions and minimum time period should be as follows:

- Long term =  $5 \pm 3^\circ$ ; 12 months
- Accelerated =  $25 \pm 2^\circ$  and  $60\% \pm 5\%$  RH; 6 months

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, which 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 retest or expiry date for a dietary ingredient that should eventually be supported with data from long-term stability studies.

If significant change occurs between 3 and 6 months of testing at the accelerated storage condition, the proposed retest or expiry period should be based on the real time data available during the long-term storage condition. If significant change occurs within the first 3 months

of testing at the accelerated storage condition, consideration should be given to address the effect of short-term excursions outside the label storage condition, such as during shipping and handling.

Preliminary shelf-life (expiry) dates can be based on pilot scale batches if the pilot batch is at least one-tenth the size of the commercial batch size and the pilot batches employ 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 ingredients being closely related in composition may be grouped together using one representative dietary ingredient formulation with which to obtain stability data to support the retest or expiry date of all dietary ingredient formulations within that group. Under such circumstances, sufficient scientific justification should be provided as to support grouping of the dietary ingredients for stability purposes.

The design of the stability studies may also bracket dietary ingredients in a way that only dietary ingredients 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 ingredients packaged in different container–closure systems (e.g., HDPE containers, aluminum canisters). In certain cases, stability data using one type of container–closure system may be used to support the stability of the product in a different type of container–closure system (e.g., HDPE versus PET container) 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 as necessary) 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 such little degradation and variability that it is apparent the product will meet specifications throughout the proposed retest or 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 retest or expiry date for the dietary ingredient. A stability report should be prepared for the dietary ingredient stating the proposed storage conditions and retest or expiry date of the dietary ingredient(s), along with the stability data and its evaluation.

## 7.9 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, when 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
- 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 should be issued for each batch of dietary ingredients. The certificate of analysis should list the name and item code of the dietary ingredient, the batch number, the date of manufacture, the date tested and released, recommended retest date, analytical method reference for each attribute, and the expiry date. The certificate of analysis also 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 certificate of analysis should be dated and signed by authorized quality unit personnel. For certificates of analysis issued for external use, the name, address, and telephone number of the manufacturer should be listed.

## 7.10 Laboratory Operations and Controls Documentation

The following documentation must be made and kept for fulfilling the requirements of the laboratory controls quality system (see 1. General Provisions).

### 7.10.1 WRITTEN PROCEDURES

Written procedures for laboratory operations must be established and followed for the following:

- The tests and examinations conducted to determine whether specifications are met
- Establishment, review, and approval of material specifications
- Preparation, review, and approval of written test procedures
- Validation and verification of test procedures for their intended use
- Selection, preparation, and handling of reagents and reference standards
- Establishment, review, and approval of sampling plans, including reduced sampling inspections
- Sampling, testing, approval, and rejection of materials, and recording and storage of laboratory data

- Investigation of deviations or OOS test results
- Establishment and implementation of a stability-testing program

## 7.10.2 RECORDS

Records must be made and kept for the following:

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

## GLOSSARY

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

**Acid foods or acidified foods:** Any foods that have an equilibrium at a pH of 4.6 or below.

**Adequate:** Item/area/system/knowledge that meets basic minimum requirements that are needed to accomplish intended purpose in keeping with good public health practice.

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

**Adverse event:** Any undesirable experience associated with the use of a food or dietary ingredient 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 food or dietary ingredient, and one or more adverse events.

**Affiliate:** Any facility that controls, is controlled by, or is under common control with another facility.

**Allergen:** A major food allergen as defined in section 201(qq) of the FD&C Act, and can be 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 either any highly refined oil derived from a food specified in 1) and any ingredient derived from such highly refined oil, or a food ingredient that is exempt under paragraph (6) and (7) of section 403(w) of the FD&C Act.

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

**Article:** Substances (e.g., raw materials, other ingredients, in-process material, dietary ingredients), consumer products (e.g., foods or dietary ingredients), and materials (e.g., 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, such as assessing a supplier's food safety processes and procedures.

**Batch:** A specific quantity of a dietary ingredient 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 ingredients can be determined.

**Blanching:** Except for tree nuts and peanuts, a prepackaging heat treatment of foodstuffs for an adequate time and at an adequate temperature to partially or completely inactivate the naturally occurring enzymes and to effect other physical or biochemical changes in the food.

**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.

**Certificate of Analysis:** A document relating specifically to the results of testing a representative sample drawn from the batch of material.

The certificate of analysis 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 (CFR):** The annual codification of the general and permanent rules and regulations published in the Federal Register by the executive departments and agencies of the US federal government. It is structured into 50 subject matter titles; Title 1 applies

to general provisions, while 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) is 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 ([www.ecfr.gov](http://www.ecfr.gov)), which is updated daily.

**Component:** Any substance intended for use in the manufacture of a dietary ingredient that appears in the finished batch of the dietary ingredient.

**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 ingredient.

**Contact surface:** Any surface that contacts a raw material, other ingredient, in-process material, or dietary ingredient, and those surfaces for which drainage can occur either to or from the raw material, other ingredient, in-process material, or dietary ingredient, and which occurs during the normal course of operations. Examples of contact surfaces include containers, utensils, tables, contact surface of equipment, and packaging material.

**Contamination:** The undesired introduction of a biological (including allergenic), chemical (including radiological), or microbiological nature, or of foreign matter, into or onto a raw material, other ingredient, in-process material, or dietary ingredient 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 (or correction):** An action that is developed and implemented to ensure that any identified root cause of a nonconformity does not reoccur. Also, an action to identify and correct a problem that occurred during the production of dietary ingredient but without other actions associated with a corrective action procedure (e.g., action to reduce the likelihood that the problem will reoccur, evaluation of all affected food for safety, and prevention of affected food from entering commerce).

**Critical:** 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 ingredient meets its specification.

**Critical control point:** A point, step, or procedure in a food process at which control can be applied and is essential to prevent or eliminate a food safety hazard or reduce such hazard to an acceptable level.

**Design qualification (DQ):** 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, and unavoidable defect at which the FDA may regard a food product as "unadulterated" and subject to enforcement action under section 402(a)(3) of the FD&C Act.

**Deviation:** Departure from an approved instruction or procedure or from an established standard (i.e., a failure, or OOS 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 to supplement the human diet by increasing the total dietary intake; a concentrate, metabolite, constituent, or extract; or a combination of any of the listed 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 to supplement the human diet by increasing the total daily intake; or a concentrate, metabolite, constituent, extract or combination of the aforementioned ingredients. It is intended for ingestion in a tablet, capsule, powder, softgel, gelcap, or liquid form; it is not represented for use as a conventional food or as a sole item of a meal or the diet; it is labeled as a dietary supplement. It does include an article approved as a new drug, certified antibiotic, or licensed biologic, and was marketed as a dietary supplement or food prior to such approval, certification, or license, unless the Secretary of Health and Human Services had issued a regulation finding that the article is unlawful when used as or in a dietary supplement under the conditions of use and dosages set forth in the labeling.

**Disposition decision:** A decision to approve or reject material, QC, and manufacturing related processes or documents, based on a scientifically valid reason. Disposition decisions can be made regarding the release of raw materials, in-process materials, dietary ingredients, packaging materials, labels, and returned dietary ingredients, based on a determination of whether or not established specifications are met, or made regarding reprocessing treatments and in-process adjustments, master production and control records, batch production and control 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 the adulteration of a dietary ingredient.

**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 procedure, product, 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, log books, instrument printouts).

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

**Environmental pathogen:** A pathogen capable of surviving and persisting within the manufacturing, processing, packing, or holding environment so that it could contaminate food and may result in foodborne illness if that food is consumed without treatment to significantly minimize the environmental pathogen. Examples of environmental pathogens include *Listeria monocytogenes* and *Salmonella* subspecies but do not include the spores of pathogenic spore-forming bacteria.

**Expiry (use by) date:** The date after which the dietary ingredient will no longer meet applicable specifications of identity, strength, quality, and purity when stored under labeled conditions.

**Facility:** A place, amenity, utility, or piece of equipment provided for a particular purpose. Also, a domestic facility or foreign facility that is required to register under section 415 of the FD&C Act, in accordance with the requirements of 21 CFR Part 1, Subpart H.

**Farm:** A primary production farm is an operation under one management in one general (but not necessarily contiguous) physical location devoted to the growing of crops, the harvesting of crops, the raising of animals (including seafood), or any combination of these activities. In addition to these activities, a primary production farm may pack or hold raw agricultural commodities, may pack or hold processed food, or may manufacture/process food under certain conditions defined in 21 CFR 1.227.

**Federal Food, Drug, and Cosmetic Act (FD&C Act):** The official compilation and codification of the federal statutes of the United States that gives authority to the FDA to oversee the safety of food, drugs, medical devices, and cosmetics (21 USC §§301–392).

**Food:** As defined in section 201(f) of the FD&C Act, 1) articles used for food, dietary supplements, or drink for man or other animals, 2) chewing gum, and 3) articles used for components of any such article. Food includes raw materials, other ingredient, and dietary ingredients.

**Harvesting:** Activities that are traditionally performed on farms for the purpose of removing raw agricultural commodities from the place they were grown or raised and preparing them for use as food. Harvesting applies to farms and farm-mixed-type facilities, and is limited to activities performed on raw agricultural commodities or on processed foods created by drying/dehydrating a raw agricultural commodity without additional manufacturing/processing on a farm. Harvesting does not include activities that transform a raw agricultural commodity into a processed food as defined in §201(gg) of the FD&C Act.

**Hazard:** Any biological (including microbiological hazards such as parasites, environmental pathogens, and other pathogens), chemical (including radiological hazards, substances such as pesticides and drug residues, natural toxins, decomposition, unapproved food or color additives, and food allergens), or physical agent (such as stones, glass, and metal fragments) that has the potential to cause illness or injury.

**Hazard requiring a preventive control:** A known or reasonably foreseeable hazard for which a person knowledgeable about the safe manufacturing, processing, packing, or holding of food would establish and manage one or more preventive controls to significantly minimize or prevent that hazard in food and raw materials and other ingredients. These controls are based on the outcome of a hazard analysis (which includes an assessment of the severity of the illness or injury if the hazard were to occur and the probability that the hazard will occur in the absence of preventive controls), and are managed (e.g., monitoring, corrections or corrective actions, verification, and records) as appropriate to the food, the facility, and the nature of the preventive control and its role in the facility's food safety system.

**Holding:** Storage of food, including incidental activities performed for that storage (e.g., activities performed for the safe or effective storage of food, such as fumigating food during storage, and drying/dehydrating raw agricultural commodities when the drying/dehydrating does not create a distinct commodity). Holding also includes activities performed as a practical necessity for the distribution of food (e.g., blending of the same raw agricultural commodity and breaking down pallets) but does not include activities that transform a raw agricultural commodity into a processed food as defined in §201(gg) of the FD&C Act. (A holding facility could include warehouses, cold storage facilities, storage silos, grain elevators, and liquid storage tanks.)

**Ingredient:** Any substance that is used in the manufacture of a food or dietary ingredient and that is intended to be present in the finished batch of the food or dietary ingredient.

**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 ingredient 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 ingredient.

**In-process tests:** Tests that may be performed during the manufacture of the dietary ingredient rather than as part of the formal battery of tests, which 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 and is properly installed in the selected environment, and that the environment is suitable for the instrument.

**Known or reasonably foreseeable hazard:** A biological, chemical (including radiological), or physical hazard that is known to be or has the potential to be associated with the facility or the food.

**Label:** A display of written, printed, or graphic matter on the immediate container of a dietary ingredient.

**Labeling:** All labels and other written, printed, or graphic matter on any dietary ingredient or any of its containers or wrappers, or accompanying such dietary ingredient at any time while the dietary ingredient 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 ingredient. It extends to documentation such as posters, tags, pamphlets, circulars, booklets, brochures, and fillers.

**Lot:** A batch or a specific identified portion of a batch (identified by an establishment's specific code) 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 raw materials, production, packaging, labeling, QC testing, release, storage, and distribution of dietary ingredients and related controls.

**Material:** A general term used to denote raw materials, in-process materials, dietary ingredients, and packaging and labeling material.

**Microorganisms:** Yeast, molds, bacteria, viruses, and other microscopic organisms having public health or sanitary concern. These include undesirable species that may have public health significance, that may cause a raw material or dietary ingredient to decompose, that indicate that a raw material or dietary ingredient is contaminated with filth, or that otherwise may cause a raw material a dietary ingredient to be adulterated.

**Monitor:** A means to conduct a planned sequence of observations or measurements to assess whether control measures are operating as intended.

**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):** 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.

**Other ingredients:** Substances that are added to a dietary ingredient preparation that are not intended or expected to be a dietary ingredient. Other ingredients are substances other than the dietary ingredient(s) that have been appropriately evaluated for safety and are intentionally included in a preparation to do one or more of the following: aid in the manufacture of a dietary supplement; protect, support, or enhance stability, bioavailability, or consumer acceptability; assist in product identification; and/or enhance any other attribute of the overall safety or delivery of the dietary ingredient during storage or use. The term is sometimes used synonymously with the terms "inactive ingredients", "pharmaceutical excipients", and "food ingredients".

**Packing:** Placing food into a container other than packaging the food. Packing includes repacking and activities performed incidental to packing or repacking a food (e.g., activities performed for the safe or effective packing or repacking of that food, such as sorting, culling, grading, and weighing or conveying incidental to packing or repacking), but does not include activities that transform a raw agricultural commodity into a processed food.

**Packaging:** Placing food into a container that transforms a dietary ingredient into a processed food or dietary ingredient.

**Packaging material:** Container and/or closure for raw materials, other ingredients, in-process material, and dietary ingredients.

**Pathogen:** A microorganism of public health significance.

**Performance qualification (PQ):** 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 ingredient.

**Preparation:** Combining, admixing, or diluting one or more dietary ingredients with or without other ingredients. The term is sometimes used synonymously with the term "premix".

**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:** Risk-based and reasonably appropriate procedures, practices, and processes that a person knowledgeable about the safe manufacturing, processing, packing, or holding of food would employ to significantly minimize or prevent the hazard identified under the hazard analysis. Preventative controls are consistent with the current scientific understanding of safe food manufacturing, processing, packing, or holding at the time of analysis.

**Preventive controls-qualified individual:** A qualified individual who has successfully completed training in the development and application of risk-based preventive controls at least equivalent to that received in a standardized curriculum recognized as adequate by the 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 ingredient.

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

**Product complaint:** Any written, electronic, or oral communication that contains any allegation or expression of concern, for any reason, with the quality of a dietary ingredient 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 by using tests for assay or content.

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

**Qualified auditor:** A qualified individual who has the technical expertise obtained through education, training, or experience (or a combination thereof) necessary to perform the auditing function and who may be a government employee, including a foreign government employee, or an audit agent of a certification body that is accredited in accordance with ISO 17020 or in accordance with the regulations in 21 CFR part 1, subpart M.

**Qualified individual:** A person who has the education (or combination thereof) necessary to manufacture, process, pack, or hold clean and safe food as appropriate to the individual's assigned duties. A qualified individual may be, but is not required to be, an employee of the establishment.

**Quality:** A standard meaning that the raw materials, in-process materials, packaging materials, labeling and dietary ingredients meet established specifications for identity, purity, strength, and composition, as well as limits on contaminants, and that the dietary ingredient has been manufactured, packaged, labeled, and held under conditions to prevent adulteration.

**Quality assurance (QA):** The sum total of the organized arrangements made with the goal of ensuring that all dietary ingredients 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 that firm to be responsible for the duties relating to QA.

**Quality control (QC):** A planned and systematic operation or procedure necessary to ensure the quality of the dietary ingredient by checking or testing that specifications are met, and taking all actions necessary to prevent the dietary ingredient from being adulterated.

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

**Quality unit (or personnel):** An organizational unit independent of production, which fulfills both QA and QC responsibilities, which 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.

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

**Raw material:** A general term used to denote starting materials, reagents, and solvents intended for use in the production of in-process materials (or intermediates) or dietary ingredients.

**Records:** Documents stating results achieved or providing evidence of activities performed (e.g., training records, executed batch production and control 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 on 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 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 Reference Standard).

**Reference standard, secondary:** A substance of established quality and purity, as shown by comparison to a primary reference standard, that is 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:** The method to introduce clean and uncontaminated raw materials and other ingredients or dietary ingredients back into the manufacturing process and to repeat a step or other appropriate physical manipulation step (e.g., milling, packaging) that is 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.

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

**Retest date:** The date when a material should be re-examined to ensure that it is still suitable for use.

**Reworking:** The method to subject in-process material or dietary ingredients 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 in order to obtain acceptable quality in-process material or dietary ingredients.

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

**Safe-moisture level:** A level of moisture low enough to prevent the growth of undesirable microorganisms in the finished dietary ingredient under the intended conditions of manufacturing, processing, packing, and holding. The safe-moisture level for a dietary ingredient is related to its water activity. Water activity will be considered safe for a dietary ingredient if adequate data are available that demonstrate that the dietary ingredient at or below water activity will not support the growth of undesirable microorganisms.

**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 (i.e., pathogens), 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 that requires a medical or surgical intervention based on a reasonable medical judgment to prevent one of those outcomes.

**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 ingredient receives any report of a serious adverse event associated with the use of the dietary ingredient in the United States [see §761(a)(3) and (b)(1) of the FD&C Act (21 USC §§379aa-1(a)(3), (b)(1)].

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

**Significantly minimize:** A reduction to an acceptable level, including elimination.

**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 raw material, in-process material, and/or dietary ingredient will meet the listed acceptance criteria when tested according to the listed test procedures. 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 ingredient. Strength only applies to a dietary ingredient.

**Subsidiary:** Any company that is owned or controlled directly or indirectly by another company.

**Supplier:** The establishment that manufactures/processes the food and raises the animal or grows the food provided to a receiving facility without further manufacturing/processing by another establishment, except for further manufacturing/processing that consists solely of the addition of labeling or similar activity of a *de minimis* nature.

**Supply-chain-applied control:** A preventive control for a hazard in a raw material or other ingredient when the hazard in the raw material or other ingredient is controlled before its receipt.

**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, and heating, ventilation, and air conditioning.

**Validation:** A documented program that provides a high degree of assurance that a specific process, method, or system will consistently produce a result that meets per-determined acceptance criteria. Also a means in obtaining and evaluating scientific and technical evidence that a control measure, combination of control measures, or the FSP as a whole, when properly implemented, is capable of effectively controlling the identified hazards.

**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 process runs, and acceptable test results.

**Verification:** 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 FSP.

**Water activity:** A measure of the free moisture in a substance or material and is the quotient of the water vapor pressure of the substance divided by the vapor pressure of pure water at the same temperature.

**Written procedures for receiving raw materials and other ingredients:** Written procedures that ensure raw materials and other ingredients are received only from suppliers approved by the receiving facility (or, when necessary and appropriate, on a temporary basis from unapproved suppliers whose raw materials or other ingredients are subjected to adequate verification activities before acceptance for use).

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

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

**Yield, theoretical:** The quantity of material that would be produced at any appropriate step of production or during packaging and labeling of a particular dietary ingredient, based on the quantity of raw materials, other ingredients, packaging, and labeling to be used, in the absence of any loss or error in actual production or packaging and labeling.

**APPENDIX**

**Reference Table: Sections of 21 CFR Used in This Chapter**

Section of (2740)	21 CFR
2. QUALITY MANAGEMENT	
2.2 Organization and Personnel	§§117.4(a)(1) and (2), 111.105(a)–(b), 111.12(a)–(c), 111.12(b), 111.113(c), 117.180(a), 117.180(b)–(d)(1) and (2), 111.13(a), 117.4(b)(2)(d); 111.10(a)(1) and (2), 117.10(a), 111.10(b)(1)–(9), and 117.10(b)(1)–(9)
2.3 Documentation and Records	§§111.605(a)–(c) and 111.610(a)–(b)
2.5 Deviations and Material Reviews	§§111.103, 111.140(b)(1)(3)(i)–(viii), 111.87, 111.113(a)–(b)(1)–(2), 111.77(a), and 111.140(b)(2)(i)–(ii)
2.7 Hazard Analysis and Risk-Based Preventive Controls (HARPC)	§§117.126(a)–(b)(1)–(7), 117.130 (a)–(c)(1)–(2), 117.135(a)–(c)(1)–(6), 117.405(a)(2)(b)–(c), 117.410(a)(1)–(4)(b)(1)–(4)(c)–(d)(1)(i)–(iii)(a)–(c)(iv)(e), 117.430(a)(f), 117.435(a),(b)(c)(1)–(2)(d), 117.415(a)–(c), 117.475(b)(c)(1)–(18), 111.105(b), 117.139(a)–(b), 117.150(a)(1)(2)(b), 117.155(a)–(b), 117.160(a)–(c), 117.165(a)–(b), 117.170(a)–(f), and 117.190(a)(2)–(6)
2.9 Complaints	§§111.553, 111.570(b)(1)–(2),111.560(a)(1)–(2)(b)(c), 111.135, 117.410(a)(1)–(2), (b)(1)–(4) and (d), 117.420(a), 117.430(a), and 117.425; §111.105(b)
2.12 Quality Management Documentation	§§111.14(b)(1), 111.103, 111.140(b)(1)–(2), 111.553, 111.570(b)(1)(2), 117.305(a)–(f), 117.310(a)7(b), 117.315(a)(1)(b)–(d), and

Section of (2740)	21 CFR
	117.330(a)-(b)
<b>3. Physical Plant and Equipment</b>	
3.1 Grounds Maintenance	§§111.15(a)(1)-(5) and 117.20(a)(1)-(4)
3.2 Physical Plant Design	§§111.20(a)(b), 117.20(b)(1), 111.20(b)(2), 111.310, 111.20(c), 117.20(b)(4), 117.20(b)(4)(6)(d), and 111.20(b)(3)(i)-(iv)(5)(7)(d)-(f)(h)
3.3 Physical Plant Sanitation and Facilities	§§111.15(b), 117.35(a)(b)(1)(i)-(iv)(2)(c)(d)(1)-(3)(e)-(f), 117.37(a), 111.15(e)-(g)(j), 117.37(b)(1)-(5)(c)(f)(d)(e)(f), 117.80(c)(6), 111.15(g)(h)(i)(j)(k), and 117.20(b)(2)
3.4 Equipment, Instruments, and Utensils	§§111.27(a), 117.40(a)(1)(c)(d), 111.27(a)(2)(3)(6)(7)(i)-(v)(4)(5)(d)(2)-(7), 117.40(a)(2)(6)(b)(e)(f), 111.30(a)-(b), 117.80(c)(1), 117.40(g)-(f), 111.27(b)(c)(d)(1)(4), and 111.605(c)
3.5 Physical Plant and Equipment Documentation	§§111.16, 111.23(b)(c), 111.25(a)-(c), and 111.35(b)(1)(i)(ii)(2)-(4)(6)
<b>4. Materials Management Operations and Controls</b>	
4.1 Establishing Material and In-Process Production Specifications	§§111.70(a)(b)(1)-(3), 117.80(b)(2)-(4), 111.70(c)(1)-(3)(d)(e)(f)(g), and 117.110(a) and (b)
4.2 Determining Compliance with Specifications	§§111.73, 111.75(a)(1)(2)b(1)(2)(c)(1)(2)-(4)(e)f(1)(2)(g)(h)(1), 117.77(a)(b)(c), and 111.90(a)(1)-(2)(c)
4.3 Receiving and Release of Materials	§111.155(a)(b)(c)(1)(d)(1)(2)(e), 111.160(a)(b)(e), 117.80(b)(1), and 111.165(a)(b)(c)(1)-(3)(d)(1)(2)(e)
4.4 Representative Samples and Reserve Samples	§§111.80(a)-(c) and 111.83(b)(2)-(4)
4.5 Holding, Distribution, and Transportation	§§111.453, 111.455, 111.460 (a)-(b), 117.80(b)(5)-(8), 111.465(a)(1)(2)(b), 111.170, 111.370, 111.510, 111.515, 111.520, 111.525, 111.530, 111.470, 1.908(a)(2)(3)(i)(ii)(c)-(e)(1), and 1.912
4.6 Materials Management Operations and Controls Documentation	§§111.475(b)(1)-(4), 111.503, 111.535(b)(1), 111.95(b)(1)-(4), and 111.140(b)(2)
<b>5. Production Operations and Controls</b>	
5.1 Master Manufacturing Records	§§111.205(a)(b) and 111.210(a)-(g)(h)(1)-(5)
5.2 Executed Batch Production Records	§§111.255(a)-(c) and 111.260(a)-(n)
5.3 Manufacturing Operations Production and Process Controls	§§111.353, 111.355, 111.360, and 117.80(a)(4)(c)(3)-(4)(8)(10)-(12)(14)-(15)
5.4 Quality Unit Responsibilities for Production	§111.123(a)(1)-(6)
5.5 Disposition Decision for Production	§§111.123(b)(1)-(4) and 117.80(c)(9)
<b>6. Packaging and Labeling Operations and Controls</b>	
6.2 Packaging Materials	§§111.410(a) and 117.80(c)(1)
6.4 Labeling Issuance and Control	§§111.415(h) and 111.410(b)

Section of (2740)	21 CFR
6.5 Packaging and Labeling Operations	§§117.80(c)(13), 111.415(a)-(h), 111.410(b)-(d), 111.83(b)(3)(4), and 111.425
6.6 Repackaging and Relabeling	§111.420(a)-c)
6.7 Packaging and Labeling Operations and Controls Documentation	§§111.403 and 111.430(b)
7. Laboratory Operations and Controls	
7.1 General	§§111.310(a)-(c), 111.315, and 111.320
7.3 Scientifically Validated Test Procedures	§§111.75(h)(1), 111.320(a)-(b), and 117.80(a)(5)
7.4 Test Procedures	§111.75(h)(2)
7.7 Out-of-Specification (OOS) Investigations	§111.75
7.10 Laboratory Operations and Controls Documentation	§111.325(b)(1)(2)(i)-(ii)

▲ (USP 1-May-2022)

**Auxiliary Information** - Please [check for your question in the FAQs](#) before contacting USP.

Topic/Question	Contact	Expert Committee
<2740> MANUFACTURING PRACTICES FOR DIETARY INGREDIENTS	<a href="#">Binu Koshy</a> Scientific Liaison	NBDS2020 Non-botanical Dietary Supplements

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