USP Ingredient Verification Program for Dietary Ingredients

Manual for Participants

Notice

This manual provides information to dietary ingredient manufacturers who intend to participate in the United States Pharmacopeia Ingredient Verification Program for Dietary Ingredients (USP IVP-DI or Program).

The Program is designed to assist participants in assuring their customers – dietary supplement manufacturers and others – that the manufactured dietary ingredient is produced in a facility that has implemented Good Manufacturing Practices (as defined in this manual), and the participant's other quality controls and systems meet all Program requirements. Program participants are solely responsible for ensuring compliance with applicable federal, state, and/or local laws and regulations. USP considers the Program to be a cooperative effort between USP and participants, and USP welcomes suggestions for improvements to the Program. Participants who meet the requirements of this Program will receive permission to use a special USP Verified Mark for use in conjunction with a certificate of analysis, container label, and marketing materials. Barring safety concerns or other special circumstances (see section 16, Mark Usage Suspension, Product Recalls and Appeals), USP maintains the confidentiality of information gained through the verification process in accordance with the provisions of the Program License Agreement, provided separately.

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1. Overview

The USP Ingredient Verification Program for Dietary Ingredients (USP IVP-DI or Program) is one of several public health programs of the United States Pharmacopeia (USP). Participation is voluntary and open to manufacturers of dietary ingredients for use in dietary supplements. Based on the legal definition in the United States, USP considers dietary ingredients to include vitamins, minerals, amino acids, herbs or other botanicals, dietary substances for use by man to supplement the diet by increasing the total dietary intake, or concentrates, metabolites, constituents, extracts, or combinations of any of the aforementioned ingredients that are used in dietary supplement products.

The Program includes a general conformity assessment as follows:

- Quality systems audit of each manufacturing site for compliance with Good Manufacturing Practices (GMPs), according to 21 CFR Part 117 *Current Good Manufacturing Practice, Hazard Analysis and Risk-Based Preventive Controls for Human Food*, and *USP-NF* general chapter <2750> *Manufacturing Practices for Dietary Supplements*.
- Product quality control and manufacturing evaluation of targeted dietary ingredients submitted for verification, including review of characterization, stability, and/or release data for compliance with labeling and certificate of analysis claims; review of critical quality attributes and the corresponding control mechanisms of the critical quality attributes for the finished product; the understanding and application of appropriate control mechanisms for the drivers of the critical quality attributes; and product conformance to the *United States Pharmacopeia* and the *National Formulary* (*USP–NF*), *Food Chemicals Codex* (*FCC*), *European Pharmacopoeia* (*PhEur*), *British Pharmacopoeia* (*BP*), *Japanese Pharmacopoeia* (*JP*), *Chinese Pharmacopeia* (*ChP*), and *Indian Pharmacopeia* (*IP*) monographs, as applicable.
- Laboratory testing of targeted dietary ingredient samples from selected lots for compliance with labeling, certificate of analysis claims, and Program requirements.
- Granting of the USP Verified Mark upon full satisfaction of Program requirements.
- Annual quality systems audit of each manufacturing site for continued compliance with GMPs.
- Annual post-verification surveillance evaluation of quality control and manufacturing documentation for dietary ingredients bearing the USP Verified Mark for continued compliance with Program requirements.

- Annual post-verification surveillance testing of targeted dietary ingredients bearing the USP Verified Mark for continued compliance with labeling and certificate of analysis claims for identification, strength, purity, and quality.
- Reporting by participants of changes to the quality control and manufacturing information for dietary ingredients bearing the USP Verified Mark.

The use of the distinctive USP Verified Mark is granted to dietary ingredients that successfully meet Program requirements. The mark indicates the verification of dietary ingredient quality by a trusted and established independent authority – USP. It provides visible assurance that

- The participant understands the necessary quality elements of the verified dietary ingredient and operates its raw material acquisition, production, and product release activities to ensure that the material consistently meets requirements.
- The participant has established and is following a quality system that helps ensure that the verified dietary ingredient meets its labeling or certificate of analysis claims for identification, strength, purity, and quality, and is consistent in quality from batch to batch.
- The participant follows accepted GMPs in producing the verified dietary ingredient.
- The tested dietary ingredient samples conform to their specification and meet requirements for acceptable limits of contaminants and impurities.

2. Requirements, Process and Submissions

Participants in the USP IVP-DI commit to doing the following:

- Complete and comply with all the contractual provisions of the Program License Agreement.
- Comply with all Program requirements set forth by USP in this publication, entitled *USP Ingredient Verification Program for Dietary Ingredients Manual for Participants*.
- Submit requested dietary ingredient samples, data, and documentation.
- Subject their dietary ingredients and facilities to all reviews, audits, tests, and other requirements specified in the Program.
- Abide by the decisions made by USP and its designees in accordance with the rules and requirements of the Program.
- Operate in accordance with the provisions of all applicable laws and regulations.
- Ensure that dietary ingredients submitted for verification meet the requirements specified in *USP–NF*, *FCC, PhEur, BP*, *JP*, *ChP*, *IP*, and/or other compendia, where applicable.
- In the absence of *USP–NF* or FCC, or other compendial standards for such dietary ingredients, ensure that adequate data are submitted for substantiation of the quality of the dietary ingredients and that there are validated analytical procedures in place to perform the necessary tests. Note that participants will be encouraged to work with USP to establish standards where none exist.
- Pay all fees required by USP agreements or by documents executed between the participant and USP.
- Act in compliance with the *Mark Usage Manual*, which provides (a) rules regarding the placement of the mark on dietary ingredient labeling and certificates of analysis, and (b) guidelines for advertising.

Companies that wish to participate in the Program shall:

- Submit an application for each manufacturing site with the list of selected dietary ingredients and the corresponding requested information at https://www.usp.org/verification-services/ingredient-verification-program
- Provide authorized signature approval for the estimated price quote letter that is prepared based on information provided in the submitted application in order to initiate execution of a License Agreement.
- Appoint a duly authorized representative to execute a License Agreement with USP.
- Provide the following financial and legal information, upon request:
    1. Description of any litigation related to the dietary ingredient(s) for which verification is sought, and a description of any pending or threatened litigation against the participant
    2. Description of general liability and product liability insurance, including limits expressed in U.S. dollars
    3. Results of audits performed by government regulatory agencies during the past three years, including the U.S. Food and Drug Administration (FDA)
    4. List of countries in which the participant is licensed to do business
    5. Copies of all relevant permits, approvals, and certificates of insurance, as required by the Program License Agreement
- Provide the list of dietary ingredient(s) for which verification is sought, with the lot history dating back six months and covering at least three lots of the dietary ingredient(s) manufactured under the current quality system.
- Submit initial GMP quality systems facility audit documentation as described in section 6.
- Submit to on-site GMP quality systems facility audits as described in section 7.
- Provide corrective action responses to audit observations/nonconformities with evidence that corrective actions have been completed.
- Provide USP with representative sample aliquots of the dietary ingredient(s), as described in section 8.

- Submit the following documentation for the product Quality Control and Manufacturing (QCM) evaluation as described in section 8, as requested by USP staff, and/or have the documentation available for review during an on-site audit, including but not limited to:

    1. General information and characterization

        a. Chemical and physical characterization: structure, crystallinity, state of aggregation, and other characteristics, as appropriate

        b. Impurities characterization, including process-related impurities and those derived from the raw material used in manufacturing

        c. Concomitant constituents (i.e., characteristic minor constituents) and/or added components, including data to justify their presence, if applicable

    2. Specifications for raw materials used to produce the products submitted for verification

    3. Release testing results for raw material lots used to produce the product lots submitted for verification

    4. Specifications for packaging and labeling materials used to package the products submitted for verification

    5. Release testing documentation for packaging and labeling material lots used to package the product lots submitted for verification

    6. Manufacturing process flow chart with inputs and outputs delineated

    7. Master production and packaging batch record(s) for the product(s) submitted for verification

    8. Executed production and packaging batch records for the product lots submitted for verification

    9. Documentation associated with any in-process test results

    10. Finished product specifications for the dietary ingredient

    11. Finished product release testing documentation and supporting data for the product lots submitted for verification, including

physical, chemical, and microbiological test results and raw data supporting the results for the submitted product lots

12. Dietary ingredient in-line, on-line, and at-line test results and supporting data when used for finished product release

13. Data on reference standards used in release testing of the dietary ingredient, and documentation on the reference standard's suitability for use

14. Test procedures used in release testing of the finished product, and supporting validation/verification test protocols, data, and reports

    a. Full validation data and reports are not necessary for *USP–NF* compendial test procedures. However, data verifying the compendial test procedure's suitability for use for the manufacturer's dietary ingredient must be included in the product QCM documentation package (see *USP–NF* general chapter ⟨1226⟩ *Verification of Compendial Procedures* for requirements).

    b. Full validation data and reports are necessary for non-compendial (i.e., manufacturer) test procedures and must be included in the product QCM documentation package (see *USP–NF* general chapter ⟨1225⟩ *Validation of Compendial Procedures* for requirements).

15. Report of results of stability studies used to support the retest or expiry date of the dietary ingredient (see the International Conference on Harmonization (ICH) Q1A(R2) *Stability Testing of New Drug Substances and Products* for guidance).

16. Regulatory status documentation: Submission of regulatory status information may need to be provided demonstrating that the dietary ingredient as either a "New Dietary Ingredient" or a "pre-DSHEA dietary ingredient" under section 413(d) of the FD&C Act. (A "pre-DSHEA dietary ingredient" means a dietary ingredient that was marketed in the United States in a dietary supplement before October 15, 1994). These data may be reviewed by USP staff with the appropriate regulatory knowledge and experience. USP staff will review the information to confirm that there is reasonable expectation that the ingredient can be considered a dietary ingredient (as defined in section 1), but this review does not make any

conclusive determination about the legal or regulatory status of the dietary ingredient in the U.S. or elsewhere.

a. For a “New Dietary Ingredient” (NDI), information should be provided demonstrating that the dietary ingredient has been either 1) the subject of a New Dietary Ingredient Notification (NDIN) properly submitted to the FDA without objection, 2) the subject of a Generally Recognized As Safe (GRAS) notice covering its intended use and submitted to the FDA and accepted without questions, or 3) documented to be GRAS for its intended use in food through a self-GRAS affirmation.

b. For a “pre-DSHEA dietary ingredient” or an “old dietary ingredient” (ODI), it may be necessary to submit information demonstrating 1) that a dietary supplement that contained the dietary ingredient was marketed in the U.S. before October 15, 1994, and/or 2) that the dietary ingredient was marketed for use in a dietary supplement before October 15, 1994.

17. Safety status documentation: Safety information may need to be submitted to demonstrate that there is a reasonable expectation that the dietary ingredient is safe for human use under stated conditions of use. These data may be reviewed by USP staff with the appropriate toxicological knowledge and experience. USP staff will review the information to confirm that there is a reasonable expectation that the dietary ingredient is safe for human use under stated conditions of use, but this review does not make any conclusive determination about the safety of the dietary ingredient’s use in dietary supplements.

    a. For “pre-DSHEA dietary ingredients” and for dietary ingredients that were the subject of a self-GRAS evaluation, safety and toxicology data demonstrating that the article is safe for human use may be required to be included in the submitted documentation.

    b. Submission of safety information may not be necessary if a *USP–NF* monograph is available for the article, because the safety of the article will have been evaluated by the appropriate USP Expert Committee. In such cases, USP staff will review the prior admission evaluation to determine whether the intended use level

and safety considerations remain comparable with typical use levels considered at the time of the admission evaluation.

18. Food Safety Plan: a set of written documents that is

    1) based upon food safety principles,

    2) incorporates hazard analysis and preventive controls, and

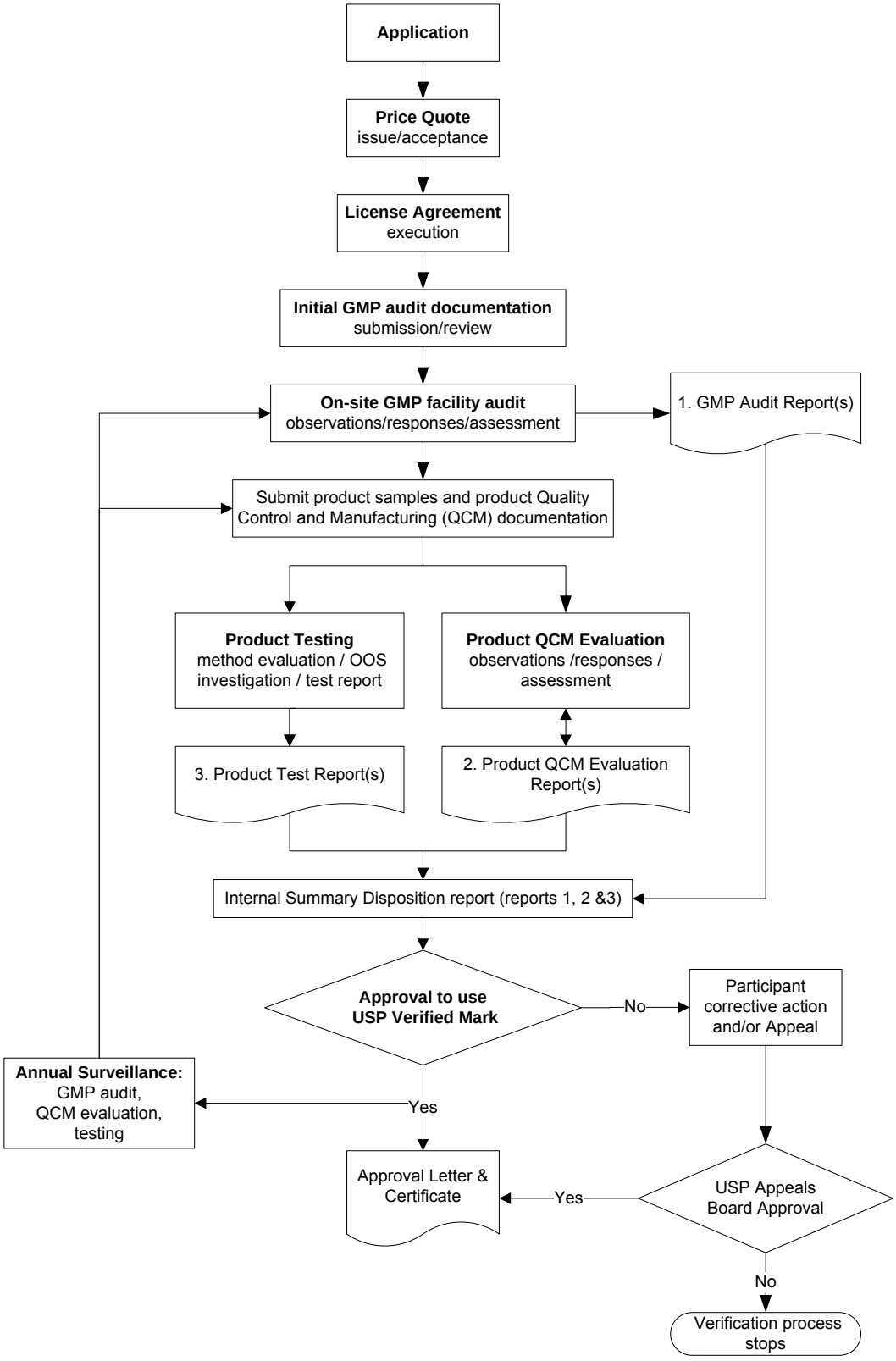
    3) delineates monitoring, corrective action, and verification procedures to be followed, including a recall plan.

- Provide corrective action responses to product QCM documentation evaluation observations/nonconformities with evidence that corrective actions were completed.

Please note that all submissions to the Program must be in English, except where noted otherwise. Translations of documents not originally created in English must be certified by the participant. A statement signed by a company representative attesting to the accuracy and completeness of the source document would suffice.

3. Process Overview Flowchart

Summary Of Verification Process



4. Product Acceptance

The company needs to submit an application form to USP for each manufacturing site, listing the dietary ingredients for which verification is being sought, along with a copy of the specifications for each dietary ingredient. USP staff will review the list of dietary ingredients and their specifications to confirm that the dietary ingredients are appropriate for inclusion in the Program. USP reserves the right to exclude dietary ingredients from the Program if there are potential concerns with verification, e.g., safety-related issues, regulatory issues, or technical issues.

Dietary ingredients meeting one or more of the following criteria may be eligible for participation in the Program:

- Dietary ingredients that have monographs in the current *USP–NF* or *FCC*
- Dietary ingredients for which monographs have been proposed in *Pharmacopeial Forum* (*PF*) or *Food Chemicals Codex Forum* (*FCCF*), *or* are in press for publication in *PF* or *FCCF*
- Dietary ingredients for which monographs are under development by the appropriate USP Expert Committee
- Dietary ingredients for which no *USP–NF* or *FCC* monograph exists but for which there is a monograph in the *PhEur, BP*, *JP*, *ChP*, *IP*, or other pharmacopeia, as applicable
- Dietary ingredients that have GRAS status under U.S. law, either as the subjects of GRAS notices submitted to the FDA and accepted without questions, or because of documentation as GRAS ingredients in food through self-GRAS affirmations
- NDIs that were not marketed in the United States in a dietary supplement before October 15, 1994, for which 75 day premarket notifications were submitted to the FDA, according to 21 CFR 190.6, without objection
- Dietary ingredients for which monographs appeared in previous revisions of the *USP–NF* but are not in the current revision and are used in finished products approved for marketing in countries other than the United States
- In certain circumstances, dietary ingredients used in products approved for marketing in countries with less stringent regulatory authorities, for which toxicology data demonstrating that the article is safe for human use is provided with the submitted application form, as described in section 2

Dietary ingredients whose monographs have been removed from the *USP–NF* because they were banned from use in the United States due to safety concerns of the FDA will not be considered for admission into the Program, even if they are used in legally marketed finished products in other countries.

Although USP may consider information related to the regulatory status of a dietary ingredient during the product acceptance phase, such an assessment is conducted for the limited purpose of determining acceptance into the Program and does not constitute a determination of the regulatory status of the article in question.

Upon execution of the License Agreement, the participant submits the description of the lot number coding system and the dietary ingredient lot history (lot number, month of manufacture, manufacturing facility, and lot size) to USP for all lots of the dietary ingredients submitted for verification that were manufactured over the past 6 months (or longer such that at least 3 lots can be identified) under the current quality systems. For the dietary ingredient(s) under consideration, the participant also submits the list of recalled lots, if any, in the past five years.

5. Product Categorization

If a participant is submitting one of dietary ingredient for verification, USP will select 3 lots of the dietary ingredient to use for the verification process. The lots will be selected randomly based on the 6-month lot history for the dietary ingredient and the availability of the dietary ingredient lots for sampling. The lots will be selected from those that are manufactured at regular commercial scale. No lots manufactured under pilot scale or research and development scale will be accepted.

If a participant is submitting a large number of dietary ingredients of a similar type, USP will attempt to categorize the dietary ingredients into groups according to scientific and quality principles with the intent to cover all unique and variable aspects of the dietary ingredients. The categorization can be based on a number of factors, including but not limited to the manufacturing site location(s), personnel, and GMP quality system(s); the manufacturing process unit operation(s) for the dietary ingredients; the chemical and physical characteristics of the dietary ingredients; and the intended use of the dietary ingredients. The participant may provide an initial categorization of the dietary ingredients for USP's review and consideration. The following table provides some examples of dietary ingredient categorization based on the chemical characteristics of the dietary ingredients.

Dietary Ingredient Type	Ingredient Categorization
Vitamins	Each vitamin will be considered a separate ingredient. Different ester or salt forms of the vitamin may be considered in the same category. For example, vitamin A acetate and vitamin A palmitate may be considered in the same category, and thiamine hydrochloride and thiamine mononitrate may be considered in the same category. Niacin and niacinamide will be considered in different categories.
Minerals	Each mineral element will be considered a separate ingredient. Different inorganic salts of the same mineral element may be considered in the same category. For example, calcium carbonate, calcium gluconate, and calcium citrate may be considered in the same category. All organometallic compounds will be considered in different categories.
Amino acids	Each amino acid will be considered a separate ingredient in a separate category.
Herbs or botanicals	Different species of the same genus will be considered different ingredients. Within the same species, different powdered plant parts and extracts will be considered different ingredients. Powdered plant parts and corresponding extracts from the same species may be considered in the same category.
Other dietary substances	Other dietary substances, concentrates, metabolites, constituents, extracts, or combinations of dietary ingredients will be considered separate ingredients in separate categories.

The number of dietary ingredients selected from each product group for initial verification will be determined based on the square-root of N plus one (√N + 1), where N is the number of dietary ingredients in the group, but not less than 3 will be selected per group. If the number of dietary ingredients in the group is less than 3, then all of the dietary ingredients in the group will be selected for initial verification. Within each product group, USP will select a minimum of 3 lots of dietary ingredient for initial verification. Dietary ingredients not chosen for initial verification will undergo an initial abbreviated quality control and manufacturing documentation review and full post-verification surveillance testing for conformance to their specifications as described in sections 9 and 10, respectively.

6. Initial GMP Quality Systems Facility Audit & Food Safety Plan Documentation

Prior to the initial on-site facility GMP audit, the participant needs to provide USP with a copy of the documents listed below. Before conducting the audit, USP staff will review the initial GMP quality systems facility audit documentation to ascertain information about the participant's quality systems and critical manufacturing processes.

The GMPs are a prerequisite foundational system that should be in place before developing the Food Safety Plan (required by law for products marketed in the U.S.), which is the primary document that guides the participant's preventive controls food safety system. Food Safety Plans are specific to a facility with preventive controls specific to the dietary ingredient and manufacturing process. Consequently, USP may review the participant's Food Safety Plan during both the GMP quality systems facility audit (section 7) and the product QCM evaluation (section 9).

The initial GMP audit documents listed below are organized according to the six GMP quality systems. In evaluating the initial GMP audit documentation, the absence of any of the following listed elements will constitute nonconformities for which the participant needs to take corrective action prior to the start of the on-site audit. If the participant's native language is not English and the standard operating procedures are not in English, the SOPs listed in **bold text** need to be translated into English for review by USP. All other SOPs can be provided in the participant's native language.

Initial GMP Quality Systems Facility Audit Documentation (6-Quality Systems Framework)

1) Quality Management System ensures overall compliance with GMPs and internal procedures and specifications.
   - **Quality policy**
   - **Quality manual**
   - **Table of contents for all company SOPs**
   - Employee training program SOP
   - **Organizational chart**
   - Job description for the key quality unit staff and the key manufacturing/operations staff
   - Personnel hygiene SOP
   - Documentation control and records keeping SOP
   - **Corrective action preventive action (CAPA) program SOP**
   - Complaint handling SOP
   - **Deviation and failure investigations SOP**
   - Recalls SOP
   - **Change control SOP**

- Internal audit program

2) Facilities and Equipment System includes activities that provide an appropriate physical environment and resources used in the production of products.
    - **Plant/site map**
    - Pest control SOP
    - Facility cleaning and sanitation SOP
    - Purified water system diagram
    - Equipment maintenance, calibration and cleaning SOP
    - Equipment cleaning validation SOP
    - Computer validation, backup, change control, and security for GMP applications SOP

3) Material System includes measures and activities to control raw material, intermediates, finished products, packaging materials (i.e., containers and closures), and labels, including validation of computerized inventory control and storage processes and distribution controls.
    - Receipt, sampling, storage, and release of raw/starting materials, packaging materials, labels, and finished product SOP
    - Specifications for components, containers, and labels SOP
    - **Supplier qualification program SOP**
    - Rejected and returned product management SOP

4) Production System includes measures and activities to control the manufacturing of products, and to perform in-process sampling and testing, and manufacturing process validation.
    - **Flowchart of manufacturing process**
    - Master production and control records SOP
    - **Manufacturing process validation SOP**
    - Reprocessing and/or reworking SOP
    - Contract manufacturer qualification SOP

5) Packaging and Labeling System includes measures and activities to control the packaging and labeling of products.
    - Master packaging and control records SOP
    - Label control SOP
    - Packaging and labeling SOP

6) Laboratory Control System includes measures and activities related to testing raw materials, starting materials, intermediates, and finished products for conformance to specifications.

- Receipt, storage and documentation of reagents, reference standards, and samples SOP
- Instrumentation maintenance and calibration SOP
- Laboratory test procedures SOP
- Analytical method validation or verification SOP
- **Out-of-Specification (OOS) investigation SOP**
- Stability program SOP

Site Master File: If the participant has prepared a Site Master File or a Type IV Drug Master File (DMF) or similar document for submission to regulatory agencies, USP may accept it as part of the aforementioned information. The Site Master File or Type IV DMF should contain general information about the site, personnel, premises and equipment, documentation, production, laboratory quality control, contract manufacture and analysis, distribution, complaints and product recall, regulatory inspections, and self-inspections.

Initial FDA Food Safety Modernization Act (FSMA) Requirements

The participant needs to meet applicable FSMA requirements including:

- Implementation of a program to comply with Hazard Analysis and Risk-Based Preventive Controls for Human Food (HARPC) under 21 CFR 117, Subpart C
- Implementation of a Supply-Chain Program under 21 CFR 117, Subpart G (if applicable)
- Compliance with Sanitary Transportation requirements under 21 CFR 1, Subpart O
- Implementation of a Foreign Supplier Verification Program under 21 CFR 1, Subpart L (if applicable)
- Implementation of Food Defense mitigation strategies under 21 CFR 121.

The HARPC includes the requirement to prepare and implement a written Food Safety Plan that will be overseen by one or more Preventive Controls Qualified Individuals (PCQIs). The scope of HARPC 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 food. FDA's draft guidance *Hazard Analysis and Risk-Based Preventive Controls for Human Food: Guidance for Industry* should be consulted.

1) Food Safety Plan
    - Hazard analysis
        - Hazard identification
            - Biological, chemical (including allergens), and physical hazards

- Hazard evaluation
    - Formulation of the food
    - 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 of food
    - Sanitation, including employee hygiene
    - Any other relevant factors
- Preventive controls
    - Critical control points (CCPs)
    - Process controls
    - Food allergen controls
    - Sanitation controls
    - Supply-chain controls (see below)
    - Recall plan
    - Other controls such as hygiene training and GMPs
- Monitoring process controls
- Corrective actions and correction procedures
- Verification and validation procedures
- Associated records

FSMA requirements also include:

- Supply-chain controls for raw materials and ingredients for which a hazard that requires supply-chain-applied control has been identified
- Requirements for sanitary transportation practices to prevent raw material and ingredients from becoming adulterated during transportation
- Risk-based mitigation strategies to protect against the intentional adulteration of food at vulnerable points of the supply chain.

2) Supply-Chain Controls
    - Risked-based supplier verification activities
        - Analysis of hazard(s) requiring supply-chain-applied control
        - Review of supplier's performance and relevant food safety records
        - On-site audits
        - Sampling and testing of raw materials
    - Use of approved suppliers
    - Verification of activities performed by other entities
    - Records

3) Sanitary Transportation Controls
    - Vehicles and transportation equipment
        - Design, maintenance, and storage
    - Transportation operations
        - Conditions and controls for safety
    - Procedures and requirements

- Shippers, receivers, loaders, and carriers
- Training
- Associated records

4) Mitigation Strategies to Protect Food Against Intentional Adulteration
   - Qualification of individuals
   - Food defense measures and plan
     - Vulnerability assessment
     - Mitigation strategies
     - Monitoring
       - Corrective actions
       - Verification
     - Procedures
     - Reanalysis
   - Associated records

Major or minor nonconformities observed during review of the initial GMP quality systems facility audit documentation and Food Safety Plan will be addressed during the on-site audit, and if necessary, cited in the on-site audit report. (As previously noted, some aspects of the participant's Food Safety Plan may also be reviewed during the product QCM evaluation process, discussed in section 9). If USP staff and/or contract reviewers observes a critical nonconformity that indicates that the participant is not apt to pass the GMP quality systems facility audit, the participant will be requested to address the critical nonconformity before USP proceeds with the on-site audit. For example, if the participant does not have a formally established program for a certain quality system element or a Food Safety Plan, the participant can provide a description of its informal process along with a proposed plan and a schedule to formalize it. Once it is formalized, USP can proceed with scheduling the GMP on-site audit.

7. GMP Quality Systems Facility Audit Process

USP staff auditors and/or approved contract auditors perform the on-site GMP quality systems audit of the participant's facilities and operations. The on-site GMP quality systems facility audit will be conducted annually.

At its sole discretion, USP may conduct an additional on-site GMP audit as a follow-up to a GMP audit when Action Level 1 critical nonconformities are observed (see section 11 for a description of Action Levels) or on a for-cause basis such as in response to a major change to the facility/site (see section 14 for classification of changes) as part of USP's post-verification surveillance activities, described in section 15. USP also reserves the right to perform an on-site audit at the participant's expense if the QCM evaluation and/or testing results raise questions regarding the current manufacturing practices that are followed by the staff on site.

Participants are also expected to conduct internal audits on an annual basis according to their internal procedures.

At USP's sole discretion, the audit may be performed unannounced or with notice at a date and time mutually agreed upon by USP and the participant. For scheduled audits, USP will communicate the agenda at least two weeks in advance to the participant's designated contact person, specifying all relevant areas and activities to be audited. The participant must ensure the availability of the required personnel.

The auditors will evaluate the findings of the on-site GMP quality systems facility audit, according to the following two requirements:
1. FDA 21 CFR Part 117 Current Good Manufacturing Practice, Hazard Analysis, and Risk-based Preventive Controls for Human Foods, subpart B Current Good Manufacturing Practice
2. USP–NF general chapter <2750> Manufacturing Practices for Dietary Supplements

The auditor will use a six-quality system-based scheme for auditing the manufacturing of dietary ingredients, including the following systems:

- Quality Management System, which ensures the overall compliance with GMPs and internal procedures and specifications
- Facilities and Equipment System, which includes the activities that provide an appropriate physical and sanitary environment and resources needed for the manufacturing of dietary ingredients
- Materials System, which includes the measures and activities used to control the starting material, raw materials, intermediates, finished products, packaging materials and labels including validation of computerized inventory control and storage processes, and distribution controls

- Production System, which includes the measures and activities used to control the manufacturing of dietary ingredients and to perform in-process sampling and testing, and manufacturing and cleaning process validation
- Packaging and Labeling System, which includes the activities used to control the packaging and labeling of finished dietary ingredients
- Laboratory Control System, which includes the activities and controls related to testing starting materials, raw materials, intermediates, and finished product for conformance to specifications, including laboratory procedures, analytical methods development, validation and/or verification, and dietary ingredient stability studies

The auditors also will evaluate the findings of the evaluation of the HARPC Food Safety Plan, supply-chain controls (as applicable), sanitary transportation controls, and mitigation strategies to protect food against intentional adulteration, according to the following three sets of regulations:

1. FDA 21 CFR Part 117 Current Good Manufacturing Practice, Hazard Analysis, and Risk-based Preventive Controls for Human Foods, subpart C Hazard Analysis and Risk-Based Preventive Controls, and subpart G Supply Chain Program
2. FDA 21 CFR Part 1 General Enforcement Regulations, subpart O Sanitary Transportation of Human and Animal Food
3. FDA 21 CFR Part 121 Mitigation Strategies To Protect Food Against Intentional Adulteration

Auditors will apply the following criteria:

Organization/Personnel

- Dedicated quality assurance/quality control department, with PCQI(s)
- Training program for the competency of all employees, including hygiene and food safety training

Quality Assurance System

- System to ensure dietary ingredient quality prior to release
- Qualification of suppliers of material and services
- Corrective action preventive action program
- Complaint handling
- Distribution records
- Recall program
- Change control management
- Annual product reviews
- Self-inspection

Document Management

- Procedures for control of SOPs, production records, analytical procedures, and specifications that include required approvals and revision/archival control, where appropriate

Electronic Records/Computerized Systems

- Proof of performance
- Appropriate security
- Appropriate backup

Equipment/Facilities

- Plant and grounds maintenance
- Adequate security to prevent access of unauthorized personnel
- Pest control
- Adequate size and design of equipment and facilities
- Sanitary facilities and controls
- Equipment qualification, maintenance, cleaning, and sanitation to ensure consistent performance for its intended use
- Documentation of use, calibration, cleaning, sanitation, and preventive maintenance of equipment

Sample/Component Control

- Program for receipt, quarantine, disposition, release, retention, and distribution of incoming materials; sample tracking from receiving through analysis in the laboratory
- Designation of the status of all raw/starting materials, manufactured intermediates, and finished dietary ingredients
- System of material reconciliation

Validation/Verification

- Process validation for dietary ingredients submitted to the Program for verification
- Equipment cleaning validation
- Validation/Verification of test procedures

Deviations

- Maintenance of deviation logs
- Policy with time frame for the disposition of deviations
- SOP for investigating and analyzing nonconforming results and trends
- Reprocessing and reworking procedures

Label Control

- Program for controlling label revision

- Program for monitoring and use of incoming labels
- Assurance of label accountability
- Monitoring of regulations, as required

Laboratory Controls

- Written analytical procedures and acceptance criteria
- Use of compendial procedures, where applicable
- Use of validated/verified and appropriate test procedures
- Review of data and analyst qualifications
- Monitoring/tracking of media/reagents prior to use
- Appropriate maintenance and calibration of laboratory equipment/instruments
- Out-of-specification (OOS) policy and procedures

Stability

- Program to evaluate dietary ingredient stability
- Testing within defined time frames
- Formal program for resolution of discrepancies in testing
- Data to support retest date of dietary ingredients submitted to the Program for verification

The on-site audit will be conducted following the example GMP quality systems facility audit agenda described in section 18, Appendix C. Upon completion of the on-site audit, USP will evaluate the on-site audit findings and summarize them in an audit report, which will include a list of any observations/nonconformities. The audit report will then be sent to the participant along with the Program's report of any actions that the participant needs to take to correct the observations/nonconformities.

The participant will have 60 calendar days to reply to reported observations/nonconformities with a corrective action plan. Failure to do so may result in discontinuation of the verification process. For Action Level 1 critical nonconformities (see section 11), proof of appropriate corrective action taken with the date of completion or progress made must be submitted to USP before the verification process can continue for the dietary ingredient. For Action Level 2 major nonconformities, the verification process will continue, but proof of appropriate corrective action taken with the date of completion must be submitted to USP before the verification letter can be issued indicating that the dietary ingredient is verified. For Action Level 3 minor nonconformities, proof of appropriate corrective action taken, with the date of completion or a commitment to implement appropriate corrective action within a specified acceptable time period, must be submitted to USP before the verification letter can be issued indicating that the dietary ingredient is verified.

8. Submission of Product Samples and Documentation

Submission of Product Samples

Sample aliquots from the selected dietary ingredient lots may be collected during the on-site audit and shipped by Program representatives to the appropriate laboratory. Alternatively, USP may request that the participant obtain representative sample aliquots of the dietary ingredient lots and ship them via the most expedient and appropriate courier services to USP. In both cases, USP staff will provide the participant with a sample request and tracking form indicating the product name(s), item code(s) and lot numbers, the quantity of sample requested, and the address of the USP office where the samples should be sent. The participant is requested to complete the form and submit it to USP along with the samples, certificate of analyses, specifications, and Safety Data Sheets (SDSs).

Dietary ingredients submitted to the Program should be sampled according to the participant's approved sampling plan and packaged either in the commercial packaging or in a suitable (e.g., similar, more portable, biocompatible) container-closure system. The container needs to be labeled with, at minimum, the following information:

- Participant's name
- Dietary ingredient name
- Dietary ingredient item code number
- Dietary ingredient lot number
- Date sampled
- Sampler's initials
- Quantity of dietary ingredient

Submission of Product Quality Control and Manufacturing (QCM) Documentation

The participant must submit the Quality Control and Manufacturing (QCM) product documentation, as specified below by USP, for the chosen lot(s):

1. General Information and Characterization
    a. Chemical and physical characterization: structure, crystallinity, state of aggregation, and other characteristics as appropriate
    b. Impurities characterization, including impurities that are process related and that are derived from the raw material used in manufacturing
    c. Concomitant constituent(s) (i.e., characteristic minor constituents), and/or added components including data to justify its (their) presence, if applicable

2. Raw material specifications for raw materials used to produce the products submitted for verification

3. Raw material release testing results for raw material lots used to produce the product lots submitted for verification

4. Packaging and labeling material specifications for packaging and labeling materials used to package and label the products submitted for verification

5. Packaging and labeling material release testing documentation for packaging and labeling material lots used to package and label the product lots submitted for verification

6. Manufacturing process diagram or flow chart with inputs and outputs delineated

7. Master production and packaging batch record(s) for the product(s) submitted for verification

8. Executed production and packaging batch records for the product lots submitted for verification

9. Documentation associated with any in-process test results

10. Finished product specifications for the dietary ingredient(s) submitted for verification

11. Finished product release test results and supporting data for the product lots submitted for verification, including physical, chemical, and microbiological test results and raw data supporting the results for the submitted product lots

12. Dietary ingredient in-line, on-line, and at-line test results and supporting data when used for finished product release

13. Data on reference standards used in release testing of the dietary ingredient and documentation of the reference standard's suitability for use

14. Test procedures used in release testing of the finished product

15. Verification data and report for compendial test procedures used for finished product release, per *USP–NF* general chapter ⟨1226⟩ *Verification of Compendial Procedures*

16. Validation protocol, data, and report for noncompendial (i.e., manufacturer) test procedures used for finished product release, per *USP–NF* general chapter ⟨1225⟩ *Validation of Compendial Procedures*

17. Report of results of stability studies used to support the retest or expiry date of the dietary ingredient [see ICH Q1A(R2) *Stability Testing of New Drug Substances and Products* for guidance].

18. Regulatory status data: see section 2, item 15 for details

19. Safety status data: see section 2, item 16 for details

The QCM product documentation should be submitted electronically to USP. In some cases, documentation might be reviewed at the participant's facility.

When many dietary ingredients are being submitted for verification, the documentation request for a dietary ingredient may not necessarily involve all sections of the documentation list. The documentation that is requested will focus on those elements that are of primary concern for a given dietary ingredient based on its chemical and physical properties. For example, in the case of an inorganic salt, the review may focus on the impurity profile (e.g., absence of elemental impurities) rather than on product stability. However, USP reserves the right to ask for full documentation.

Common Technical Document (CTD): Note that the requested information may be submitted in the format of the Chemistry, Manufacturing, and Controls (CMC) Documentation following the format of the quality section of the CTD. The CTD provides a harmonized structure and format for presenting CMC information submitted for technical review to the regulatory authorities in the United States, European Union, Japan, and/or China. The requested information should be submitted electronically.

Type IV DMF: If the participant has an existing Type IV DMF for submission to regulatory agencies, such documentation can be submitted as part of the aforementioned information format, as long as it contains all of the information required. The document should address the key elements listed in this section and should facilitate documentation for non-English speaking participants. USP staff will inform the participant if additional information is required, for example, executed batch production records may be requested if not included in a Type IV DMF. The review process may be suspended until the requested additional information has been provided to USP.

Technical Feasibility Review

For noncompendial dietary ingredients, USP staff will conduct an initial technical feasibility review of the participant's dietary ingredient specification and test methods to determine whether the information supports the ability to control the quality of the dietary ingredient being verified. The specification needs to include adequate tests for the identity, purity, strength, limits of contaminants, and performance that define the standard of quality for the material. The test procedures must be validated according to *USP–NF* general chapter ⟨1225⟩ *Validation of Compendial Procedures*. The technical

feasibility review helps ensure that USP can successfully conduct testing of the dietary ingredient(s) in USP laboratories and/or by one or more approved contract laboratories before much time, effort, and cost have been expended in the verification process for the dietary ingredient(s).

9. Product Quality Control and Manufacturing (QCM) Evaluation

USP will review all product Quality Control and Manufacturing (QCM) documentation and records submitted (see section 8) for dietary ingredients accepted into the Program. USP will determine whether the specifications (tests, analytical procedures, and acceptance criteria) provided are sufficient to demonstrate consistent and appropriate dietary ingredient quality. USP will review specifications relating to raw materials, in-process and/or intermediate materials, final dietary ingredients, packaging and labeling materials, reference materials, analytical validation data, and stability data, as well as the certificate of analysis and analytical data from the selected lots.

In some cases, the QCM documentation and records may be reviewed at the manufacturing facility during the on-site audit, or at a separate time. However, that will increase the time and resources needed to conduct the on-site audit and/or the on-site product QCM evaluation.

Raw Materials, Critical/Key Intermediates, and Final Dietary ingredients: For dietary ingredients that have a monograph in *USP–NF*, *PhEur*, *BP*, *JP*, *ChP*, *IP*, and/or other pharmacopeia, USP will verify conformance to the requirements specified in the monograph(s).
For dietary ingredients that have no compendial monographs, USP will verify that the specifications provided by the participant are adequate to ensure the identification, strength, purity, and quality of the dietary ingredients, in accordance with the labeling.
The specifications will be evaluated, as applicable, for

- Identification
- Content, strength, and/or purity of a specific entity or marker(s)
- Foreign substances and impurities (see *USP–NF* general chapter <1086> *Impurities in Drug Substances and Drug Products*)
    - Elemental impurities (see USP–NF general chapters <232> Elemental Impurities Limits and <233> Elemental Impurities Procedures)
    - Residual solvents (see *USP–NF* general chapter <467> *Residual Solvents*)
    - Known toxic impurities
    - Microbial contaminants (see USP–NF general chapter <2023> Microbiological Attributes of Nonsterile Nutritional and Dietary Supplements)
- Physicochemical properties (e.g., water, pH, melting point, optical rotation)
- Specific tests (e.g., peroxide value, anisidine value)

The specification should follow the guidelines for the preparation and appropriate use of specifications described in ICH Q6A *Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances*, and/or ICH Q6B *Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products*.

For critical/key intermediates, USP will verify that the specifications provided by the participant are adequate to ensure that the dietary ingredient meets its specification.

For critical/key intermediates purchased from contract manufacturers, participants must have a supplier qualification program in place. In general, USP will not subject these intermediates to additional testing except when the penultimate intermediate is purchased.

Applicable sections in the CTD include 1.1 Nomenclature; 1.2 Structure; 1.3 General Properties; 2.3 Control of Materials; 2.4 Controls of Critical Steps and Intermediates; 3.1 Elucidation of Structure and Other Characteristics; 3.2 Impurities; 4.1 Specifications; and 4.5 Justification of Specification.

Packaging and Labeling Materials: USP will review descriptions and specifications provided by the participant for packaging materials that are or will be in direct contact with the dietary ingredient (i.e., primary packaging materials) and secondary packaging materials, as well as samples and specifications provided for labels and labeling materials.

Reference to the *USP–NF*, FCC, other pharmacopeias, and standards on labels or labeling must be completely accurate. Labeling must comply with all applicable regulatory and compendial labeling requirements.

Applicable sections in the CTD include 1.1 Nomenclature; and 6.0 Container Closure System.

Method Validation: USP will review documentation for each analytical procedure. If the analytical procedure is found in an official compendium, there is no need for a complete validation report. In this case, the suitability of the test procedure for testing the specific dietary ingredient must be supported by analytical data (see *USP–NF* general chapter ⟨1226⟩ *Verification of Compendial Procedures*). If the analytical procedure is not in an official compendium, the procedure must be validated according to *USP–NF* general chapter ⟨1225⟩ *Validation of Compendial Procedures*.

If the validation data provided by the participant do not demonstrate that the procedure is suitable for its intended use, the process will stop until adequate validation data are provided.

Applicable sections in the CTD include 4.2 Analytical Procedures and 4.3 Validation of Analytical Procedures.

Reference Materials: For USP Reference Standards (USP RS) that have been used for their specified compendial purpose, all that is needed is the lot number of the USP RS used. For non-USP reference standards or for non-compendial uses of USP RS, the source of the material and data to support the suitability of the material for its intended use must be submitted.

Applicable sections in the CTD include 5.0 Reference Standards or Materials.

Stability Data: Procedures used in stability studies will be reviewed to determine if they are adequate for evaluating dietary ingredient quality attributes (such as appearance, content, degradation products, aggregation, and microbial counts) that are susceptible to change during storage and likely to influence the dietary ingredient's quality. Real-time stability studies will be used for review. If data from real-time stability studies are not available at the time of verification, then accelerated stability data may be acceptable, provided the participant follows up by submitting real-time stability data as they become available. ICH Q1A(R2) *Stability Testing of New Drug Substances and Products* provides recommendations on stability-testing protocols that address temperature, humidity, and trial duration.

Applicable sections in the CTD include 7.1 Stability Summary and Conclusions, 7.2 Post-approval Stability Protocol and Stability Commitment, and Stability Data.

Certificate of Analysis (CoA): USP will evaluate supporting data and verify that the analytical results on the certificates of analysis from the selected dietary ingredient lots under review and testing are in compliance with the specification proposed by the participant. The CoA should follow the guidelines for the preparation and appropriate use of a CoA detailed in *USP–NF* general chapter <1080> *Bulk Pharmaceutical Excipients – Certificate of Analysis*. In case of noncompliance, USP will provide recommendations for changes.

Applicable sections in the CTD include 4.4 Batch Analysis.

Manufacturing Documentation: USP will review all manufacturing documentation (submitted per section 8). USP will review manufacturing records, specifications provided by the participant for in-process control steps defined in the internal manufacturing and process directions, and execution of those records.

Master Manufacturing Batch Records (MMBRs):
Documentation submitted must include the following master documentation:

- Master formula(s), master manufacturing production directions, manufacturing guide, and/or packaging/labeling directions
- A process diagram of chemical synthesis, extraction, secondary/tertiary recovery, fermentation, grinding, sifting, sizing, cleaning, etc., if applicable
- Acceptable procedures for reprocessing that demonstrate that the lot meets label or certificate of analysis declarations and the stability specification; alternatively, a statement that reprocessing is not performed would suffice
- Identification of in-process steps requiring a quality control check (particularly for critical/key intermediate steps involved in synthesis, extractions, sizing, etc.)

Executed Manufacturing Batch Records (EMBRs): The documentation submitted must include the executed batch records for the lots that USP has selected for review. The executed batch records must include documentation of completion of each significant step and should include the following:

- Dates and, when appropriate, times
- Identity of major equipment (e.g., reactors, driers, mills) used
- Specific identification of each batch, including weights, measures, and batch number of raw materials, intermediates, or any reprocessed materials used during manufacturing
- Actual results recorded for critical process parameters
- Any sampling performed
- Signatures (or initials) of the persons performing and directly supervising or checking each critical step in the operation
- In-process and laboratory test results
- Actual yield at appropriate phases or times
- Description of packaging and label for the dietary ingredient
- Any deviation noted, its evaluation, and any investigation conducted (if appropriate) or reference to that investigation if stored separately
- Results of release testing
- Indication of quality assurance final release approval

Applicable sections of the CTD include 2.1 Manufacture(s); 2.2 Description of Manufacturing Process and Process Controls; 2.2.1 Alternate Processes; 4.4 Batch Analysis; and 8.0 Facilities and Equipment.

Request for Supplemental Information: If the QCM documentation is found to be unacceptable, incomplete, not in the requested format, or inadequate for any reason, USP may return it to the participant for revision and resubmission.

If the QCM documentation is considered unacceptable and USP determines, after discussion with the participant, that the evaluation of additional information or dietary ingredient samples submitted by the participant will not add useful data, the entire quality control and manufacturing documentation will be deemed unacceptable and the verification process will be discontinued.

If the QCM documentation is considered unacceptable but, based on discussion with the participant, there is sufficient justification for USP to think that the evaluation of additional information or test data/results of dietary ingredient samples submitted by the participant will add useful data, USP will review any additional supplied procedures and/or analytical test results.

The dietary ingredient samples submitted by the participant will be analyzed either in USP laboratories or in USP-approved contract laboratories. If the laboratory results support the acceptance of the QCM documentation, USP will proceed to the next step in the verification process. If the laboratory results support the acceptance of the QCM documentation but lead to other issues, a written report will be sent to the participant asking for comments and additional information. If the laboratory results do not support the acceptance of the QCM documentation, the verification process will be discontinued.

Reporting and Corrective Action Procedure
USP will report findings in a product QCM evaluation report, which will include a list of any observations and/or nonconformities. The product QCM evaluation report will then be sent to the participant along with the Program's report of any corrective actions that the participant needs to take to correct the observations/nonconformities.

The participant will have 60 calendar days to reply to reported observations/nonconformities with a corrective action plan. Failure to do so may result in the discontinuation of the verification process. For Action Level 1critical nonconformities (see section 11), proof of appropriate corrective action taken, including the date of completion or progress made, must be submitted to USP before the verification process can continue for the dietary ingredient. For Action Level 2 major nonconformities, the verification process will continue, but proof of appropriate corrective action taken, including the date of completion, must be submitted to USP before the verification letter can be issued indicating that the dietary ingredient is verified. For Action Level 3 minor nonconformities, proof of appropriate corrective action taken, including the date of completion or a commitment to implement appropriate corrective action within a

specified acceptable time period, must be submitted to USP before the verification letter can be issued indicating that the dietary ingredient is verified.

10. Testing of Product Samples

Testing of dietary ingredient samples will begin after USP has determined that the documentation regarding the dietary ingredient's specifications, test procedures with appropriate validation data/report, and the certificate of analysis are all complete and acceptable. Testing of dietary ingredient samples may occur in parallel with the product QCM documentation review.

Each dietary ingredient will be tested for critical quality attributes as determined by USP to evaluate the quality of the dietary ingredient and full conformance with its specification, label claims, and certificate of analysis.

USP will coordinate testing of dietary ingredient samples in USP laboratories and/or by one or more approved contract laboratories. A single analysis will be performed for each dietary ingredient test. Test data will then be evaluated for accuracy and to determine if the dietary ingredient conforms to its specification acceptance criteria.

If the test data obtained conform to the acceptance criteria and no other issues arise from the test results, USP will proceed to the next step in the verification process.

If the test data obtained do not conform to the acceptance criteria or if other issues arise from the test results, USP will re-evaluate the raw data submitted by the laboratory to confirm the accuracy of the test results. If specific analytical errors (i.e., determinant errors) are found, a sample retest will be requested from the laboratory. The laboratory will be asked to reanalyze the original sample, if possible in duplicate. If the reanalyzed results agree with the initial test result, all results will be averaged and reported. If the reanalyzed results confirm the suspected analytical error, only the reanalyzed results will be averaged and reported.

In the case of nonconforming results where there is no determinant error or assignable cause, the laboratory will be asked to follow its formal out of specification (OOS) investigation procedures. As part of the OOS investigation, USP staff may review the manufacturing records and consult with the participant to determine if a manufacturing error could be the potential cause for the nonconforming results.

As an example of a laboratory OOS investigation, the laboratory might reanalyze the original sample, if possible in duplicate, along with a newly submitted sample of the dietary ingredient lot, in duplicate. Ideally, different experienced analysts would perform testing on each sample set. If the four reanalyzed results disagree with the initial test result, the average of the four reanalyzed test results would be reported. If the four reanalyzed results agree with the initial test result, all results would be averaged and reported. In all cases, all results would be reported.

In all cases, the reported results will be compared to the participant's specification acceptance criteria for determining compliance with label and/or certificate of analysis claim(s). In the event of a question regarding compliance with the participant's specification acceptance criteria, label, and/or certificate of analysis claim(s), the decision by USP shall be final.

USP will issue copies of the laboratory test results to the participant for their records.

11. Classification of Observations

The status of nonconformities observed within each program element (i.e., GMP quality systems facility audit, product QCM evaluation, and product testing for conformance to specifications) may be divided into three categories: critical Action Level 1, major Action Level 2, and minor Action Level 3 observations. These three categories differ according to the nature and potential impact of the nonconformity. All action level nonconformities require some corrective action to be taken by the participant.

ACTION LEVEL 1 critical issues involve a lack of a GMP quality system program element and/or lack of an essential dietary ingredient quality attribute or criteria. Action Level 1 critical issues require major changes to the current quality system. Action Level 1 critical issues may be resolved by implementing the missing GMP quality system program element and/or by supplying the missing essential quality attribute or criteria through a major change to the dietary ingredient. Action Level 1 critical issues must be adequately resolved before the verification process can continue for the dietary ingredient and may require the manufacturing site be re-audited and/or the dietary ingredient be resubmitted for verification.

ACTION LEVEL 2 major issues involve a lack of information regarding a GMP quality system program element, or a GMP quality system requirement that is not being followed adequately, or the need to resolve an important dietary ingredient quality attribute or criteria. Action Level 2 major issues do not require major changes to the current GMP quality system, and they may be resolved by addressing the concerns regarding the GMP quality system program element and/or by resolving the dietary ingredient quality attribute or criteria through a major change to the dietary ingredient. Action Level 2 major issues must be adequately resolved before a dietary ingredient can be verified. In addition, Action Level 2 major issues may be downgraded to Action Level 3 minor issues if remedial corrective action has been taken to address the major issue of concern.

ACTION LEVEL 3 minor issues involve the need for clarifying information or newly requested information regarding a GMP quality system program element, or requested improvements to dietary ingredient quality attributes or criteria. Action Level 3 issues may be resolved by supplying requested information or by making requested improvements to the dietary ingredient quality attributes or criteria through a minor change to the dietary ingredient. Action Level 3 minor issues require a commitment from the participant to implement appropriate corrective action within a specified acceptable time period before the dietary ingredient can be verified. Failure to address an Action Level 3 issue within the specified time period may lead to the Action Level 3 minor issue being changed to an Action Level 2 major issue.

USP staff may provide the participant with Opportunities for Improvement (OFIs). An OFI just represents a suggestion for consideration that requires no response from the participant and does not adversely impact dietary ingredient verification.

12. Product Approval Process

Satisfactory completion of the items listed below for each dietary ingredient or dietary ingredient group is required for product approval:

- Evaluation of initial GMP quality systems facility audit documentation (section 6)
- Evaluation of on-site GMP quality systems facility audit report (section 7)
- Evaluation of product QCM documentation (section 9)
- Evaluation of test results for dietary ingredient samples for conformance to specifications (section 10)

For each dietary ingredient or dietary ingredient group that successfully completes the verification program requirements, USP will issue an approval letter and a Certificate of Standards Compliance. The approval letter and the certificate will specify which of the participant's dietary ingredients are entitled to the use of the USP Verified Mark and other limiting information (such as manufacturing site information) as appropriate.

USP will review all labeling that will include the USP Verified Mark for the USP-verified dietary ingredient. USP reserves the right to ask for additional documentation as necessary.

The mark must be used in accordance with the Program License Agreement and the guidelines in the *Mark Usage Manual*, which will be provided by USP along with the notification of approval to use the mark. These guidelines relate to

- Size and color of the USP Verified Mark
- Acceptable format and materials
- Specifications for reproduction
- Examples of appropriate and inappropriate use
- Acceptable and unacceptable usage of the USP Verified Mark in advertising and promotional materials, exhibit signage, and educational materials; at speaking engagements, presentations, and events; and on websites

See section 13 for further details.

13. Use of the USP Verified Mark

USP requires submission of artwork for dietary ingredient labels, advertising, promotions, or other materials that include the USP Verified Mark for pre-approval. The artwork must be submitted in final mock-up form in color along with stock (paper) samples and bindery details, if applicable. A specification sheet outlining the strategy/goals of the materials, the target audience, and the number of pieces to be produced should be provided along with the artwork. USP may also require actual production copies of artwork using the mark to be submitted for evaluation.

Written approval or disapproval of the materials submitted will be provided by USP to the participant within 10 business days. USP may, if necessary, request additional materials from the participant. Materials must conform to the recommended guidelines to be approved by USP. If the materials are not approved by USP, the participant will be given an opportunity to correct or adjust deficiencies and resubmit the materials to USP. The participant must obtain USP's final written approval before using the mark.

News releases and associated references to the Program must be submitted to USP for approval prior to release. If desired, USP will work at its discretion with the participant on joint news releases. USP will draft, edit, and coordinate approvals of the joint news releases and work with the participant to determine the media list(s) for distribution.

A list of licensed participants and licensed dietary ingredients under the Program will be made available to the public on the USP website.

If the USP Verified Mark is misused or improperly used, USP will work with the participant licensed to use the USP Verified Mark to resolve the problem(s) or any related dispute(s). USP and the licensed user will agree on a written plan to bring the usage into required conformance. However, if the problem cannot be resolved to USP's satisfaction, USP will issue a written warning of proposed revocation or suspension of the license to use the USP Verified Mark, either in its entirety or on a dietary ingredient-specific basis. The warning shall specify the steps required for the participant to come into conformance and avoid revocation or suspension of use of the mark along with a reasonable time period for achieving conformance. In the case of continued nonconformance, USP will make a final decision to revoke or suspend the participant's license to use the USP Verified Mark, either in its entirety or on a dietary ingredient-specific basis. Such a decision may not be appealed by the participant.

Participants are reminded, however, that the terms and conditions set forth in the Program License Agreement have precedence over this manual.

14. Change Notification Process

After USP has granted approval to use the USP Verified Mark, any significant change to a dietary ingredient must be reported in writing to USP. A significant change is one that alters a dietary ingredient's physical or chemical property outside the established limits. The participant should also notify USP in writing of any other change that the participant deems to be important.

The types of change that are considered here are changes to the following: site, scale, equipment, process, packaging and labeling, and specification (including raw materials).

Significant Change Evaluation Criteria
The following is a list of various criteria that are used to determine the significance of a change affecting a dietary ingredient. These include:

- Chemical properties
- Physical properties
- Essential concomitant constituents
- Moisture level, if applicable
- Bioburden, if applicable
- Origin of raw materials or contact packaging

Risk Levels
In the evaluation of the effect of changes on the dietary ingredient, it is recognized that even with objective criteria some judgment may be necessary. To facilitate the decision as to the significance of a change and the likely effect on the dosage form, the types of changes are classified using two risk levels:

Level 1: Minor Change

Level 2: Major Change

A Major Change (Level 2) is defined as a change with substantial potential to have an adverse effect on the identification, strength, quality, or purity of the dietary ingredient as those characteristics may relate to the safety or intended use of the dietary ingredient. These changes are considered likely to affect the dietary ingredient's chemical or physical properties or impurity profile. Major changes should always be communicated to users and must be communicated by the participant to USP upon implementation, but prior to commercial distribution. Such notification by the participant must be made in writing using a Program change notification form provided by USP to participants upon

request. The participant needs to provide a list of the dietary ingredients that are affected by such changes, the details of the changes, and the rationale for the changes. The notification must include data from lots manufactured prior to the change and lots manufactured after the change. Upon receipt of such notification, USP will expedite the review of such change and communicate its decision as to whether or not the participant's GMP quality system or dietary ingredient needs to be re-evaluated or the dietary ingredient retested.

A Minor Change (Level 1) is a change with minimal potential to have an adverse effect on the identification, strength, quality, or purity as those characteristics may relate to the safety and the intended use of the dietary ingredient. These changes are considered unlikely to affect the dietary ingredient's chemical or physical properties or impurity profile. Such changes should be documented, and should be communicated by the participant to USP in the Annual Product Review report (see section 15); change notification prior to implementation is not required.

Protocol Design

There should be a written protocol for the evaluation of a change to determine whether it is significant. The protocol should describe the nature of the change, the reason it may be significant, the testing to be performed to evaluate the change, and the criteria for determining the significance. Then, where possible, the results from the testing of a minimum of 10 pre- and 3 post-change batches of dietary ingredient should be compared. The manufacturer should test the dietary ingredient made after the change for all specification properties and compare the results to the historical data. A standard statistical test, such as a *t*-test of the means, should be used to compare the new data with the historical data. If when using an appropriate statistical analysis there is sufficient evidence that the batches are different at the 95% confidence interval, the change should be considered significant. As an additional check for consistency, it is also recommended that the new batch specification properties be plotted on standard Statistical Quality Control (SQC) control charts, along with standard batch results.

Supporting Data

It is preferable to use data to measure the effect of a change on the dietary ingredient. The comparison should begin with chemical and physical properties, followed by moisture, bioburden, and impurity profile where appropriate. The manufacturer should use good judgment when making sample comparisons for the other evaluations.

Chemical and physical properties lend themselves to quantitative measurement. Often these properties are part of the specification for the dietary ingredient. As such there should be a large body of test data to use for the affected properties when comparing the corresponding data for the dietary ingredient after the change.

Equivalence of impurity profiles is shown by comparing the data for the pre-change and post-change batches. If the following conditions are met, there has been no significant change in the impurity profile.

(i) No new impurity is present at or above 0.10%, nor has there been a significant change in the impurity profile.

(ii) Residual solvent and impurities remain within the 95% confidence interval of the mean of the batches produced before the change.

Documentation

It is recommended that the evaluation of changes to the dietary ingredient be documented, regardless of the level of change. The report should indicate the basis for evaluating the effect of the change on the dietary ingredient, the significance of the data used in reaching the conclusion, and the actions taken.

Where appropriate, the process validation should be updated to reflect the changed process. This is clearly indicated where the evaluation has led to the conclusion that the change should be considered a major change.

Notification

Major Changes (Level 2) must be communicated by the participant to USP upon implementation, but prior to commercialization. Such notification by the participant must be made in writing using a Program change notification form provided by USP to participants upon request. Minor Changes (Level 1) should be communicated by the participant to USP in the Annual Product Review report (see section 15); change notification prior to implementation is not required.

Upon receipt of information regarding changes, USP will review the information and determine whether it concurs with the participant's rating of the risk level, i.e., whether the changes are Level 1 or 2. The criteria for such a determination will be made available, in writing, to the participant. If necessary, USP may require the participant's GMP quality system or dietary ingredient to be re-evaluated or the dietary ingredient retested.

If re-evaluation is not required, the participant may continue to use the USP Verified Mark in accordance with licensed terms. If re-evaluation is required, USP will immediately notify the participant in writing. USP also may require the participant to cease continued use of the USP Verified Mark until the re-evaluation has been completed.

The participant may appeal the decision to require re-evaluation or retesting under the procedures described in section 16, however, the participant shall not have the right to

appeal the decision requiring it to cease using the USP Verified Mark until the final decision is made regarding the status of re-evaluation or retesting.

15. Post-Verification Surveillance

USP conducts annual post-verification surveillance activities for each of the three primary program elements (i.e., GMP quality systems facility audit, product QCM evaluation, and product testing for conformance to specifications).

Annual GMP Quality Systems Facility Audits

As previously described in sections 6 and 7, USP conducts an initial on-site GMP quality systems facility audit of the participant's manufacturing operations shortly after the company has entered the Program. Annually thereafter, USP conducts surveillance on-site GMP quality systems facility audits of the participant's manufacturing operations to help ensure that the participant continues to maintain a high level of control over the manufacturing processes at the site. An on-site GMP quality systems facility audit typically lasts 3 days; however, the surveillance audit may be shortened to a 2-day audit based on the results of the initial or previous audit and a risk-based assessment of the manufacturer's quality systems.

USP may recognize inspections carried out by regulatory agencies of countries/regions such as the United States, Canada, Japan, Europe, the United Kingdom, and Australia. In lieu of USP conducting the on-site GMP quality systems facility audit in a given year, USP may agree to review a copy of the regulatory agency's inspection report to determine whether or not the report provides sufficient information for USP to bypass the onsite GMP quality systems facility audit for the given year. Such inspection reports may be used in whole or in part to meet the Program requirements, depending on the documented coverage by the regulatory agency. The firm's responses to any observations made by the regulatory agency will be assessed using the same procedures used for a USP audit. Objective evidence will be requested for any corrective action(s). Corrective actions for observations concerning areas outside the scope of verification will be accepted by USP based on acceptance of those corrective actions by the regulatory agency. If the inspection is acceptable in part, then an abbreviated USP on-site GMP quality systems facility audit may be performed to fulfill the Program requirements. If the inspection is fully acceptable, USP would use the date of the regulatory inspection to determine the date for the next on-site audit.

At its sole discretion, USP may conduct an additional on-site GMP audit as a follow-up to a GMP audit when an Action Level 1 critical nonconformity (see section 11 for a description of Action Levels) is observed, or on a for-cause basis, such as in response to a major change to the facility/site.

Annual Product Review (APR) Reports

After the USP Verified Mark is awarded to a dietary ingredient, the participant must provide USP with an Annual Product Review (APR) report. The APR report for each verified dietary ingredient (or group of dietary ingredients) is due within 3 months after

the end of the calendar year (i.e., by March 31). If the participant's fiscal year is not on a calendar year basis, the participant can choose to submit the APR report within 1 month after the end of the participant's fiscal year. The APR report should include, but is not limited to, the following information:

- Lot numbers and manufacture dates of all batches of verified dietary ingredients manufactured during the preceding year
- List of deviations recorded in these dietary ingredients
- List of all quality-related OOS results/investigations
- List of customer complaints/recalls
- List of all changes (major and minor)

If any compliance issues arise during the review of the APR report, USP reserves the right to conduct additional on-site audits, product QCM evaluations, and/or product testing.

Annual Product QCM Evaluation and Product Testing

After the USP Verified Mark is awarded to a dietary ingredient, USP will perform at a minimum an annual evaluation of the dietary ingredient to ensure that it continues to meet the Program criteria. Participants will be required to submit samples and corresponding executed manufacturing records from their manufacturing sites to support this post-verification surveillance work. If any master manufacturing records and specifications have been revised, copies of the revised master documents need to be submitted to USP along with the executed manufacturing records.

When many dietary ingredients are being submitted for verification, the dietary ingredients evaluated during post-verification surveillance typically will be those that did not undergo full product QCM evaluation or product testing in previous years.

USP will contact the participant and request the lot history (with lot numbers and manufacturing dates) for dietary ingredients bearing the USP Verified Mark, with an indication of which lots are available to be sampled for post-verification testing. From that list, USP will randomly select a minimum of one lot for each dietary ingredient to perform post-verification testing. USP will ask the participant to send samples of the specified lot(s) to the designated USP laboratory. Alternatively, USP auditors may observe collection of samples of the lot(s) by the participant during the annual on-site GMP quality systems facility audit. In both cases, USP staff will provide the participant with a sample request and tracking form indicating the product name(s), item code(s) and lot number(s), and the quantity of sample requested. USP will also provide the

address of the USP laboratory where the samples should be sent. The participant is requested to complete the form and submit it to USP along with the samples.

USP will test the samples it receives in accordance with the compendial and/or participant's specification. Subsequently, USP will request, at a minimum, the release specification and analytical procedures used by the participant, if not previously provided. USP also may request further documentation based on the dietary ingredient that was verified. At its sole discretion, USP may perform testing beyond the testing specified by the participant and will likely do so if there is a reasonable probability that the dietary ingredient contains known contaminants or degradation products.

16. Mark Usage Suspension, Product Recalls and Appeals

USP may refuse to approve the use of the USP Verified Mark or may suspend or revoke the use of the USP Verified Mark by participants in certain situations listed below. Participants may appeal the following actions by USP:

- Rejection of initial GMP quality systems audit documentation, GMP quality systems audit results, quality control and manufacturing documentation, test results, or post-verification surveillance results
- Suspension or revocation of the USP Verified Mark
- Recommendations for product recalls

Rejection Based on Nonconformities in GMP audit results, Product QCM Documentation, or Test Results

Among other things, USP may reject as insufficient:

- Documentation that fails to meet the requirements for initial GMP quality systems facility audit documentation
- Audit reports that show critical nonconformities from GMPs at the facility
- Documentation that fails to meet the requirements for product quality control and manufacturing documentation (for initial verification and post-verification surveillance)
- Test results that fail to demonstrate that the dietary ingredient conforms to its specification or meets the labeled amount or other acceptance criteria (for initial verification and post-verification surveillance)

USP will send written notification of rejection to the participant, along with any relevant findings or reports. The participant will have the opportunity to appeal the rejection or take corrective action(s). Subsequently, if USP rejects the corrective action(s), the participant may appeal that rejection. The participant must send a written notice of appeal, along with any supporting evidence, within 30 calendar days from the date of receiving the written notification from USP.

USP's Appeals Panel (see Glossary for definition) will review the evidence received with the appeal and decide to accept or reject the participant's data and/or audit reports. In either case, written notification of the decision will be sent to the participant within 30 calendar days after receipt of participant's appeal. If the data and/or audit reports are accepted, USP will resume initial verification work at the appropriate step of the verification process, or will reinstate approval to use the USP Verified Mark, as

applicable. If the data and/or reports are rejected during the appeal, the participant can re-enter the Program after correcting the nonconformities.

Product Recalls

USP may recommend a product recall of a dietary ingredient bearing the USP Verified Mark if critical dietary ingredient nonconformities are detected. Dietary ingredient nonconformities are considered critical if

- There is a reasonable probability that the use of, or exposure to, the dietary ingredient may cause serious adverse health consequences or death when used as intended (Class I recall)
- There is a reasonable probability that the use of, or exposure to, the dietary ingredient may cause temporary or medically reversible adverse health consequences when used as intended (Class II recall)
- An official from the participant company has submitted fraudulent documents to USP
- An official organization, such as the FDA, has recommended voluntary recall
- An official organization, such as the FDA, has issued a mandatory recall order

Upon recommending a recall, USP will immediately notify the participant. Within 24 hours of such a recall recommendation, USP will convene a hearing – by conference call – with the participant's representative(s), who must answer any questions and provide the requested information about the dietary ingredient problem. USP will then affirm or reverse its recommendation to recall the dietary ingredient. If USP decides that it will recommend a recall, it will immediately contact the FDA (for product marketed in the United States), and notify the participant to discontinue the use of the USP Verified Mark on the dietary ingredient. However, if the participant immediately contacts the FDA about the product recall and provides USP with written notice that it has done so, USP will not need to contact the FDA. The participant must take immediate action to discontinue use of the USP Verified Mark, but it may appeal within seven calendar days the decision to discontinue the right to use the USP Verified Mark. The Program License Agreement requires participants to release and hold USP harmless for any reports that it files in good faith with the FDA and for any decisions USP makes regarding participants' applications for continued participation in the Program.

Suspension of the USP Verified Mark

The following examples are illustrative and do not represent an exhaustive list. USP may suspend a participant's right to use the USP Verified Mark due to

- Violation of any Program participation criteria, policies, or procedures by the participant, its affiliates, or agents
- Critical or major dietary ingredient nonconformities, which involve a major deviation from dietary ingredient standards and/or manufacturing process

USP will review information submitted by the participant for major changes (see section 14) and will determine whether or not to suspend use of the USP Verified Mark during re-evaluation or retesting of the dietary ingredient. Such work may include review of analytical data or additional audits at the participant's expense.

The participant may appeal USP's decision to suspend use of the USP Verified Mark. The appeal, along with any supporting evidence, must be made within 30 calendar days from the receipt of notification of suspension from USP. If no appeal is made within this period, the suspension becomes a revocation of the use of the USP Verified Mark and withdrawal of verification status with no further rights of appeal.

When submitting the appeal, the participant may request a review of analytical procedures data, documentation, or an audit. USP will conduct such review or audit at the participant's expense and provide a written report of findings to the participant.

The participant may, on appeal, also request an oral hearing. USP will set a place, time, and date – not more than 60 calendar days after receiving the hearing request – and will notify the participant. USP and the participant may present evidence at the hearing to a USP Appeals Panel. The participant may be represented by counsel. The chief of the Appeals Panel will preside over the hearing and determine any other procedures that will govern the hearing. The participant shall pay all reasonable expenses incurred by USP including, but not limited to, travel expenses.

The USP Appeals Panel will issue a written determination with supporting reasons within 30 calendar days, if in the hearing it is found that the participant

- Is substantially out of compliance with the Program criteria – in which case USP will revoke the participant's verification status and use of the USP Verified Mark.
- Is substantially in compliance with the Program criteria – in which case USP will reverse the suspension and reinstate use of the USP Verified Mark.
- Can conduct corrective action within six months to become substantially compliant with Program criteria – in which case USP will affirm the suspension until further review. The participant must notify USP within 30 calendar days that it will seek the review. The participant will bear the cost of such review by USP. The

participant's failure to notify USP within 30 calendar days or failure to be in substantial compliance within six months will result in revocation of verification status and use of the USP Verified Mark.

The decision of the USP Appeals Panel is final. In accordance with the Program License Agreement, participants must agree not to file a legal action challenging any such decision by USP or the USP Appeals Panel. Upon revocation of the use of the USP Verified Mark, a participant may re-enter the Program one year from such revocation, on payment of full fees.

17. Glossary

Acceptance Criteria: Predetermined limits (e.g., number, numerical range) against which sample data are compared to determine compliance with standards of quality.

Actual Yield: The quantity that is actually produced at any appropriate step of manufacture or packaging of a particular dietary ingredient.

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

Allergen Cross-Contact: The unintentional incorporation of a food allergen into a food.

Appeals Panel: A group consisting of the USP Chief Legal Officer (or designee), the USP Chief Science Officer (or designee), the USP Vice President of Quality Assurance (or designee), the Head of the Verification Programs (or designee), and additional USP staff as needed. The Panel will have the authority to review appeals submitted by companies participating in the Program regarding 1) rejection based on nonconformities in GMP audit results, product QCM documentation, or test results; 2) product recalls; or 3) suspension of the use of the USP Verified Mark.

Auditor: Any USP Program staff member or USP-approved contract auditor/ firm that performs the on-site GMP quality systems audit or product QCM evaluation.

Batch (or Lot): A specific quantity of a dietary ingredient or other material that is intended to have uniform character and quality, within specified limits, and is produced according to a single manufacturing order during the same cycle of manufacture.

British Pharmacopoeia (BP): The British Pharmacopeia is published for the Medicines and Healthcare products Regulatory Agency (MHRA) on the recommendation of the Commission on Human Medicines. It contains approximately 3200 monographs for substances, preparations, and articles used in the practice of medicine within the United Kingdom. Some of the monographs are of national origin while others have been reproduced from the European Pharmacopoeia.

Certificate of Analysis (CoA): A document relating specifically to the results of testing a representative sample drawn from the batch of material to be delivered.

Chemistry, Manufacturing, and Controls (CMC): Information submitted for a drug substance to ensure continued drug substance and drug product quality (i.e., the identity, strength, quality, purity, and potency) to support the approval of a drug application.

Chinese Pharmacopoeia (ChP): The Pharmacopoeia of the People's Republic of China, compiled by the Pharmacopoeia Commission of the Ministry of Health of the People's Republic of China, is an official compendium of drugs that covers Traditional Chinese and Western medicines. The compendium includes information on the standards of purity, description, test, dosage, precaution, storage, and strength for each drug.

Commercial Scale: The manufacture of a dietary ingredient on production manufacturing scale for commercial use.

Common Technical Document (CTD): A guideline developed by the International Conference on Harmonization (ICH) that is divided into five sections: organization/general, quality, safety, efficacy, electronic. The quality section of the CTD provides a harmonized structure and format for presenting CMC information for submission to the regulatory authorities in the United States, European Union, Japan, and China, for technical review. This document can be accessed on the ICH website (www.ich.org).

Concomitant Constituent: A substance found in a dietary ingredient that is not the intended chemical entity but that may be necessary for the proper performance of the dietary ingredient in its intended use. It is not an impurity or a foreign substance.

Critical: The lack of a GMP quality system program element and/or lack of an essential dietary ingredient quality attribute or criteria, that may cause variation in the dietary ingredient's quality attributes.

Current Quality System: The quality assurance/control system and manufacturing process in place since the last instituted major change to the dietary ingredient manufacturing operation.

Defect Action Level: The level of a non-hazardous, naturally occurring, unavoidable defect above which FDA may regard a food product "adulterated" and subject to enforcement action under section 402(a)(3) of the Federal Food, Drug, and Cosmetic Act.

Drug Master File (DMF): A Drug Master File is a submission to the Food and Drug Administration (FDA) that may be used to provide confidential, detailed information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storage of one or more human drug components. The submission of a DMF is not required by law or FDA regulation. A DMF is submitted solely at the discretion of the holder. The information contained in the DMF may be used to support an Investigational New Drug Application (IND), a New Drug Application (NDA), an Abbreviated New Drug Application (ANDA), another DMF, an Export Application, or amendments and supplements to any of these. A DMF is not approved or disapproved. The technical

contents of a DMF are reviewed only in connection with the review of an IND, NDA, ANDA, or Export Application. FDA has prepared guidelines to provide DMF holders with procedures for preparing and submitting a DMF that will be acceptable to the agency. There are five types of DMFs. Those types that are relevant to this manual from the standpoint of content, structure, and format include a Type I Manufacturing Site, Facilities, Operating Procedures, and Personnel; a Type II Drug Substance, Drug Substance Intermediate, and Material Used in Their Preparation, or Drug Product; and a Type IV Excipient, Colorant, Flavor, Essence, or Material Used in Their Preparation. The Type II and IV DMFs should follow the harmonized structure and format of the ICH CTD.

Expert Committee (EC): One of USP's scientific standards-setting bodies that are responsible for the content of *USP–NF*, the *Food Chemicals Codex*, and associated publications, that are organized into Collaborative Groups based on topics of common interest.

European Pharmacopoeia (PhEur)*:* The European Pharmacopoeia is published by the Directorate for the Quality of Medicines & HealthCare of the Council of Europe (EDQM). The monographs of PhEur, both specific and general, together with other texts made mandatory by virtue of reference in monographs, are applicable throughout the 37 Member States including the European Union itself.

Federal Food Drug and Cosmetic Act (FD&C Act): The Federal Food, Drug, and Cosmetic Act was passed in 1938 and has been expanded with subsequent amendments. It gives authority to the FDA to oversee the safety and/or efficacy of foods, drugs, medical devices, and cosmetics.

FDA Food Safety Modernization Act (FSMA): The FDA Food Safety Modernization Act was passed in 2011 and it substantially revised the U.S. food regulatory system, giving FDA broader regulatory authority and imposing new obligations on the food industry characterized by inclusion of both preventive and responsive measures to ensure the safety of domestically produced and imported foods.

Food Chemical Codex (FCC): The current official volume of the *Food Chemical Codex,* including its supplements. It contains food ingredient monographs, as defined in the *Front Matter* of *FCC*, as well as General Tests and Assays, and General Information Chapters.

Food Drug Administration (FDA): The U.S. Food and Drug Administration is part of the Public Health Service (PHS) within the Department of Health and Human Services (HHS).

Food Safety Plan: As the cornerstone of the Hazard Analysis and Risk-Based Preventive Controls (HARPC) required under FSMA, the Food Safety Plan is a set of written documents. The Plan is based upon food safety principles; incorporates hazard analysis and preventive controls; and delineates monitoring, corrective action, and verification procedures to be followed, including a recall plan.

Foreign Substance: A component that is present in the dietary ingredient but was not introduced into the dietary ingredient as a consequence of its synthesis or purification and is not necessary to achieve the proper performance of the dietary ingredient.

Generally Recognized As Safe (GRAS): A status whereby a chemical or substance added to food is considered safe by experts, and thus is exempted from the FD&C Act food additive premarket review requirements (see 21 CFR 182, 184, and 186). Under sections 201(s) and 409 of the Act, and FDA's implementing regulations in 21 CFR 170.3 and 21 CFR 170.30, the use of a food substance may be GRAS either through scientific procedures or, for a substance used in food before 1958, through experience based on common use in food. Manufacturers may "self-determine" the GRAS status of ingredients based on the review and evaluation of published scientific literature establishing the safety of the substance under intended conditions of use. There is no requirement that manufacturers notify FDA of GRAS self-determinations. However, some manufacturers voluntarily notify FDA of the GRAS status of ingredients via a Notification process. FDA does not "approve" GRAS Notifications; a positive response is where FDA reviews the submission and issues a letter indicating that the agency has "no questions" about the GRAS determination at that point in time.

Good Manufacturing Practices: The requirements found in the legislation, regulations, and administrative provisions for methods to be used in, and the facilities or controls to be used for, the manufacturing, processing, packing, and/or holding of a health-related product to assure that such health-related product meets the safety requirements of all applicable jurisdictions and has the identity and strength to meet the quality and purity characteristics that it purports or is represented to possess. GMPs are the part of quality assurance that ensures that products are consistently produced and controlled to quality standards. Different GMPs exist for drugs, dietary supplements, foods, pharmaceutical excipients, dietary ingredients, and food ingredients.

Hazard Analysis and Risk-Based Preventive Controls (HARPC): A set of requirements under FSMA starting with a hazard analysis to identify food safety hazards that must be controlled to minimize the likelihood of foodborne illness or injury, followed by the development of risk-based preventive controls to address such hazards. See 21 CFR Part 117, Subpart C.

Impurity: Any component of the dietary ingredient that is not the entity defined as the dietary ingredient or a concomitant component, but is present as a consequence of either the raw materials used or the manufacturing process and is not a foreign substance.

Impurity Profile: Description of the identified and unidentified impurities present in a dietary ingredient and their acceptance criteria.

Indian Pharmacopoeia (IP): The Pharmacopoeia of the Republic of India, compiled by the Indian Pharmacopoeia Commission (IPC), is an autonomous institution of the Ministry of Health and Family Welfare that sets standards for all drugs manufactured, sold, and consumed in India. These standards include information on the purity, description, test, dosage, precaution, storage, and the strength for each drug.

Intermediate: A material produced during steps of the manufacturing process for a dietary ingredient that undergoes further chemical or physical change before it becomes the final dietary ingredient.

International Conference on Harmonization (ICH): The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use is a unique collaborative body that brings together the regulatory authorities of Europe, Japan, China, and the United States along with experts from the pharmaceutical industry in the four regions to discuss scientific and technical aspects of product registration. ICH also makes recommendations on ways to achieve greater harmonization in the interpretation and application of technical guidelines and requirements for product registration.

Japanese Pharmacopoeia (JP): The Japanese Pharmacopoeia is published by the Society of Japanese Pharmacopoeia on behalf of the Ministry of Health, Labour and Welfare (MHLW). It provides an official standard that is required to ensure the quality of medicines in Japan.

Mark Usage Manual: A USP document that a) describes the terms, conditions, and placement for using the USP Verified Mark on dietary ingredient labels and CoAs and b) provides guidelines for advertising with the USP Verified Mark.

Must: The word “must” is used to state mandatory requirements under the provisions of this manual.

Participant: A company that has qualified to participate in the USP Ingredient Verification Program for Dietary Ingredients by signing a Program License Agreement with USP.

Pesticide Analytical Manual (PAM): FDA's *Pesticide Analytical Manual* is a repository of the analytical procedures used in FDA laboratories to examine food for pesticide residues for regulatory purposes (40 CFR 180.101 (c)). The manual is organized according to the scope of the analytical procedures and is available in print format or in Adobe Acrobat (pdf) format on the FDA's website.

Pilot Scale: The manufacture of a dietary ingredient on a reduced scale using processes that simulate and are representative of processes to be applied on a larger, production manufacturing scale.

Procedure: A detailed set of instructions (methodology) used to generate analytical data or used to perform a manufacturing operation.

Quality Manual: A quality manual describes the quality management system, the quality policy, and the commitment of the dietary ingredient manufacturer to apply the appropriate GMP and quality management standards. The manual should include the scope of the quality management system, reference to supporting procedures, and a description of the interactions between various different quality management processes.

Quality Assurance (QA): The sum total of the organized arrangements made to ensure that all dietary ingredients are of the quality required for their intended use and that quality systems are maintained.

Quality Control (QC): The inspection or testing performed to demonstrate that specifications are met.

Raw Material: Any ingredient or starting material intended for use in the manufacture of a dietary ingredient.

Recall: A participant's removal or correction of its marketed dietary ingredient, directed by USP or an official organization such as the FDA, or initiated by the participant because of a critical dietary ingredient nonconformity.

Representative Sample: A sample that consists of a number of units that are drawn from a larger set based on rational criteria such as random sampling. The objective is to ensure that the sample accurately portrays the material being sampled.

Residual Solvents: Organic volatile chemicals that are used or produced in the manufacture of dietary ingredients. They are not completely removed by practical manufacturing techniques. (See *USP–NF* general chapter <467> *Residual Solvents*.)

Retest Date: The end of the time interval during which the dietary ingredient must conform to applicable specifications when stored under labeled conditions. The retest date should be supported by stability data and should be indicated on the dietary ingredient label and exterior commercial packaging.

Shall: Used to state mandatory requirements under the provisions of the Program License Agreement.

Should: Used to state recommended or advisory actions or procedures.

Specification: A list of tests, references to test procedures, and acceptance criteria that define the standard of quality for a material to be acceptable for its intended use. Product specifications include test specifications for identity, purity, strength, limits on contaminants, and performance that define a standard of quality for a material.

Standard Operating Procedure (SOP): Detailed, written step-by-step instructions needed to perform a job or task. SOPs help to promote uniformity in the performance of technical and quality system requirements.

Stability Protocol: Documents describing the sample, test specifications, test intervals, conditions, and packaging used to determine the retest date.

Targeted Dietary Ingredient(s): Dietary ingredient(s) chosen for evaluation to represent a group of dietary ingredients that have been grouped based on (but not limited to) their chemical characteristics (e.g., chemical structure and properties), intended use, site of manufacturing, manufacturing unit operation, and/or the quality system under which they were manufactured.

Theoretical Yield: The quantity that would be produced at any appropriate step of manufacture or packaging of a particular dietary ingredient, based on the quantity of raw materials or packaging to be used, in the absence of any loss or error in actual production.

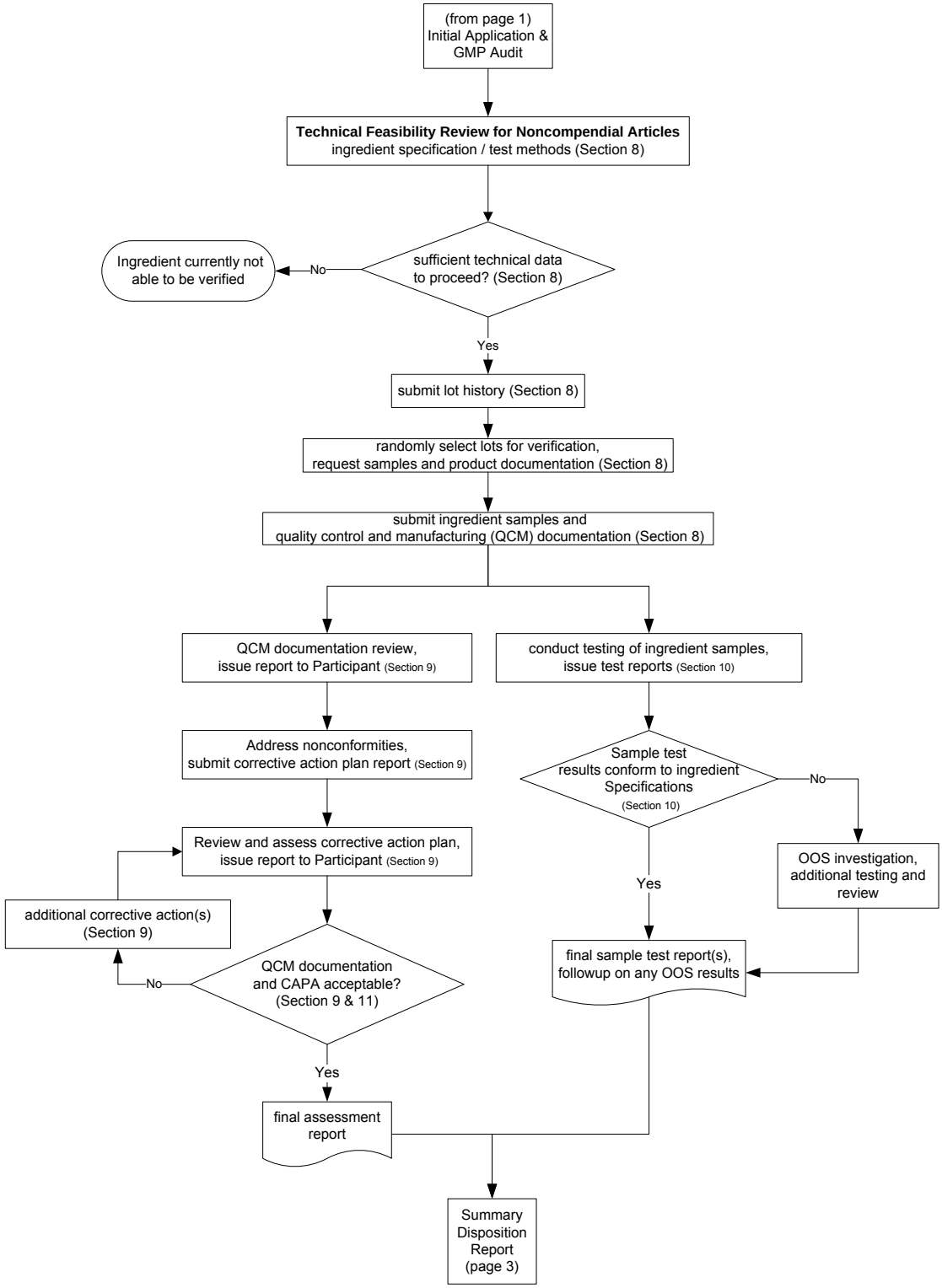
***United States Pharmacopeia–National Formulary* (*USP–NF*):** The current official volume of the *United States Pharmacopeia–National Formulary,* including its supplements. It contains official article (substance and product) monographs, as defined in the *General Notices* of *USP–NF*, as well as General Tests and Assays, and General Information Chapters. Although *USP* and *NF* are published under one cover and share *General Notices and Requirements*, they are separate compendia.

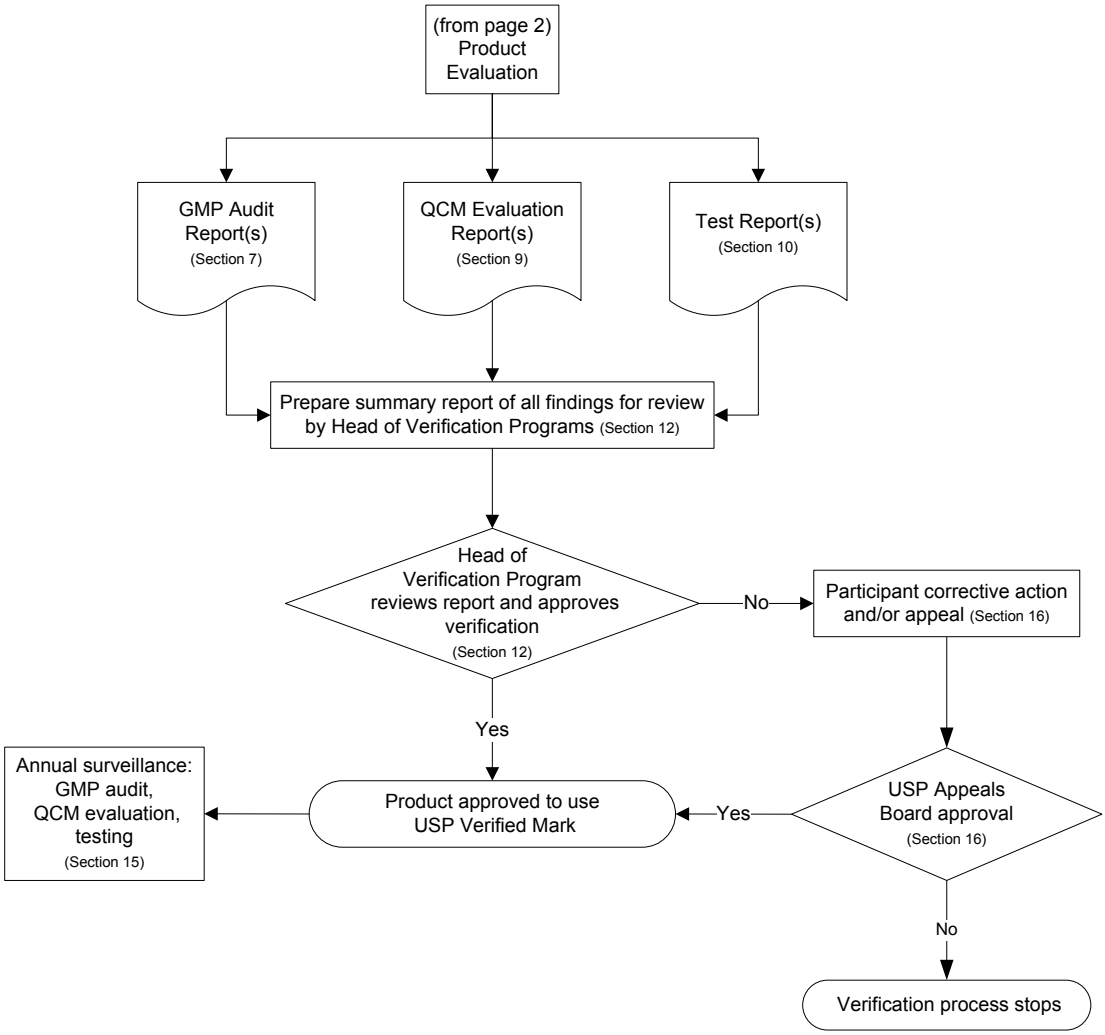
USP Reference Standard: Substances selected for their high purity, critical characteristics, and suitability for the intended purpose. They are used to test for

compliance with *USP–NF* requirements, to demonstrate identity, strength, quality, and purity of official articles.

18. Appendix

A. Detailed Process Flowcharts


(from page 1)
Initial Application & GMP Audit
Technical Feasibility Review for Noncompendial Articles
ingredient specification / test methods (Section 8)
sufficient technical data to proceed? (Section 8)
No
Ingredient currently not able to be verified
Yes
submit lot history (Section 8)
randomly select lots for verification, request samples and product documentation (Section 8)
submit ingredient samples and quality control and manufacturing (QCM) documentation (Section 8)
QCM documentation review, issue report to Participant (Section 9)
conduct testing of ingredient samples, issue test reports (Section 10)
Address nonconformities, submit corrective action plan report (Section 9)
Sample test results conform to ingredient Specifications (Section 10)
No
OOS investigation, additional testing and review
Review and assess corrective action plan, issue report to Participant (Section 9)
Yes
additional corrective action(s) (Section 9)
QCM documentation and CAPA acceptable? (Section 9 & 11)
No
final sample test report(s), followup on any OOS results
Yes
final assessment report
Summary Disposition Report (page 3)


(from page 2) Product Evaluation
GMP Audit Report(s) (Section 7)
QCM Evaluation Report(s) (Section 9)
Test Report(s) (Section 10)
Prepare summary report of all findings for review by Head of Verification Programs (Section 12)
Head of Verification Program reviews report and approves verification (Section 12)
No
Participant corrective action and/or appeal (Section 16)
Yes
Annual surveillance: GMP audit, QCM evaluation, testing (Section 15)
Product approved to use USP Verified Mark
Yes
USP Appeals Board approval (Section 16)
No
Verification process stops

B. Initial GMP Quality Systems Facility Audit Documentation

The initial GMP quality systems facility audit documentation is needed prior to USP conducting the first GMP audit of the participant's manufacturing site. The requested pre-audit documents listed below are organized according to the six GMP quality systems. If the participant's native language is not English and the standard operating procedures (SOPs) are not in English, the SOPs listed in **bold text** need to be translated to English. All other SOPs can be provided in the participant's native language.

Initial GMP Quality Systems Facility Audit Documentation (6-Quality Systems Framework)

1) Quality Management System ensures overall compliance with GMPs and internal procedures
and specifications.
    - **Quality policy**
    - **Quality manual**
    - **Table of contents for all company standard operating procedures (SOPs)**
    - Employee training program SOP
    - **Organizational chart**
    - Job description for the key quality unit staff and the key manufacturing/operations staff
    - Personnel hygiene SOP
    - Documentation control and records keeping SOP
    - **Corrective action preventive action (CAPA) program SOP**
    - Complaint handling SOP
    - **Deviation and failure investigations SOP**
    - Recalls SOP
    - **Change control SOP**
    - Internal audit program

2) Facilities and Equipment System includes activities that provide an appropriate physical environment and resources used in the production of products.
    - **Plant/site map**
    - Pest control SOP
    - Facility cleaning and sanitation SOP
    - Purified water system diagram
    - Equipment maintenance, calibration and cleaning SOP
    - Equipment cleaning validation SOP
    - Computer validation, backup, change control, and security for GMP applications SOP
3) Material System includes measures and activities to control starting materials, raw material ingredients, intermediates, finished products, packaging materials (i.e.,

containers and closures) and labels, including validation of computerized inventory control and storage processes and distribution controls.

- Receipt, sampling, storage, and release of raw/starting materials, packaging materials, labels, and finished product SOP
- Specifications for components, containers and labels SOP
- **Supplier qualification program SOP**
- Rejected and returned product management SOP

4) Production System includes measures and activities to control the manufacture of products, and to perform in-process sampling and testing and manufacturing process validation.
    - **Flowchart of manufacturing process**
    - Master production and control records SOP
    - **Manufacturing process validation SOP**
    - Reprocessing and/or reworking SOP
    - Contract manufacturer qualification SOP

5) Packaging and Labeling System includes measures and activities to control the packaging and labeling of products.
    - Master packaging and control records SOP
    - Label control SOP
    - Packaging and labeling SOP

6) Laboratory Control System includes measures and activities related to testing raw materials, starting materials, intermediates and finished product for conformance to specifications.
    - Receipt, storage and documentation of reagents, reference standards and samples SOP
    - Instrumentation maintenance and calibration SOP
    - Laboratory test procedures SOP
    - Analytical method validation or verification SOP
    - **Out-of-Specification (OOS) investigation SOP**
    - Stability program SOP

C. GMP Quality Systems Facility Audit Agenda (Example)

On-Site Audit Agenda
USP Ingredient Verification Program for Dietary Ingredients

Company: {Company Name}

Audit Dates: {Start and end date of audit}

Location(s): {Address of facility to be audited. If more than one site is to be audited, this will list facility addresses for each.}

Product(s): ***Verified Products:***

Product Code	Product Name

Products Undergoing Verification:

Product Code	Product Name

Escort(s): {Name(s) of site personnel acting as host for the audit}

Auditor(s): {Name and title of auditor}

Audit Type: Good Manufacturing Practices – Dietary Ingredient Manufacturer

Audit Standards: FDA 21 CFR Part 117 Current Good Manufacturing Practice, Hazard Analysis, and Risk-based Preventive Controls for Human Foods, subpart B Current Good Manufacturing Practice; and USP–NF general chapter <2750> Manufacturing Practices for Dietary Supplements

Audit Duration: {Typically three (3) days}

Scope: Full Audit for USP Ingredient Verification Program for Dietary Ingredients

VER Reference #: {Verification document reference barcode}

Proposed Agenda

Ideally, the audit will be conducted each day between the hours of 8:00 am and 5:00 pm; however, the auditor(s) will adapt to existing circumstances and reserves the right to modify the hours and schedule, as needed.

Opening Meeting (½ to 1 hour - repeated on the first day of the audit at each site)

- Introduction of personnel
- Purpose of the audit
- Description of manufacturing plant operations (Company presentation)
    - Organizational chart
    - Site layout
    - Overview of facility, processes, and operational capacity

Review of responses to observations resulting from the previous USP audit {insert date of previous audit}.

Review of FDA investigations / 483 observations, if any.

Plant Tour (following the process flow)

- Raw materials, packaging, and labels receipt and storage area
- Warehouse area(s)
- Production area(s)
- Purified or deionized water system and utilities area
- Label control
- Packaging area
- Laboratory area
- Bulk and finished goods control, storage, and release area

On-site lunch (each day – about ½ hour)

Based on the available time, the auditor will then conduct a spot check document/records review of several of the following six quality systems. The specific quality systems to be reviewed will be announced to the audit participants by the auditor(s) at the commencement of the on-site audit.

Note: At the end of each of the six quality system sections is a request for the firm to provide specific documentation and/or have it readily available for review. The information below is provided for guidance. The auditor will select the specific quality systems documentation to be reviewed while on site.

1) Quality Management System assures overall compliance with GMPs and internal procedures and specifications.
    - Quality manual and policy
    - Employee training program, e.g., job descriptions, training standard operating procedures (SOPs), personnel training records, qualifications and certifications, personnel hygiene
    - Documentation control and records keeping
    - Internal quality audit program
    - Corrective action preventive action (CAPA) program
    - Complaint reviews
    - Discrepancy and failure investigations
    - Recalls
    - Change control
    - Validation master plan, including protocols and reports, as applicable, for equipment qualification (IQ, OQ, PQ), manufacturing process validation, analytical method validation or verification, computer system validation, cleaning validation
    - Annual product review
    - Quality unit approval oversight
    - Contract manufacturers and laboratories

USP requests that the participant provide a copy of the quality manual and the table of contents for all company SOPs; and have readily available a list of training records, internal audits, CAPAs, customer complaints, deviations, returns, recalls, and contract manufacturers and laboratories.

2) Facilities and Equipment System includes activities that provide an appropriate physical environment and resources used in the production of products.
    - Facility and Grounds Maintenance
        - Physical plant sanitation
        - Grounds keeping
        - Pest control
        - Water supply and plumbing
        - Sewage and trash disposal
        - Bathrooms and hand washing facilities
    - Purified water system
    - HVAC system
    - Equipment
        - Construction
        - Installation, operational, performance qualification (IQ, OQ, PQ)
        - Maintenance, calibration, and cleaning procedures
        - Automated, mechanical, or electronic equipment application

- Computer system
    - Verification of GMP related applications
    - Backup, change control, and security

USP requests that the participant have readily available a plant/site map; water system diagram; a list of manufacturing equipment; manufacturing equipment calibration/maintenance/cleaning schedule; computer systems for GMP related activities.

3) Material System includes measures and activities to control raw material ingredients, other components, intermediates, containers, and labels.
    - Receipt, sampling, storage, and records of raw/starting materials, packaging materials, labels, and finished product
    - Specifications of raw/starting materials, packaging materials, and labels
    - System of release of raw/starting materials, packaging materials, and labels
    - Validation of computerized and inventory control processes
    - Storage and distribution controls
    - Supplier qualification program
    - Rejected and returned/salvaged product management

USP requests that the participant have readily available a copy of raw material, packaging material and label specifications, material handling SOPs, a list of approved suppliers, and supplier qualification records.

4) Production System includes measures and activities to control the manufacture of products.
    - Master production and control records
    - Major operations or steps in the process e.g., raw material weighing, synthesis, extraction, condensation, purification, crystallization, filtration, drying, milling/pulverizing, blending, packaging, labeling, and testing.
    - In-process sampling and testing
    - Manufacturing process validation
    - Reprocessing and reworking production and control records
    - Recovery of reactants/solvents (e.g., from mother liquor or filtrates)

USP requests that the participant have readily available a lot history for USP verified (approved or in-process) products; a copy of the master and executed production control records for selected lots; and a list of manufacturing process validation reports for USP verified products.

5) Packaging and Labeling System includes measures and activities that control the packaging and labeling of products.
    - Label control
    - Packaging and labeling of dietary ingredients

USP requests that the participant have readily available a copy of label and packaging specifications and SOPs, and the master and executed packaging control records for selected lots of USP verified (approved or in-process) products.

6) Laboratory Control System includes measures and activities related to testing raw materials and finished product for conformance to specifications.
    - Receipt, storage, and documentation of reagents, reference standards, and samples
    - Laboratory notebooks and instrument logbooks
    - Instrumentation maintenance and calibration
    - SOPs and specifications for testing
    - Laboratory test procedures
    - Out-of-Specification (OOS) investigation procedures
    - Analytical method validation or verification
    - Stability program
    - Reserve samples
    - Waste disposal of samples

USP requests that the participant have readily available a list of analytical instrumentation; analytical instrumentation IQ/OQ/PQs reports; analytical instrumentation calibration/maintenance schedule; analytical test procedures; analytical test procedure method validation/verification reports; non-conformances and out-of-specification investigations; and stability studies.

In the afternoon of the last day of the audit *(insert date):*
Auditor's caucus to prepare the closing meeting report (½ to 1 hour)
Audit Closing Meeting (about ½ hour)

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