



USP Dietary Supplement Verification Program

Manual for Participants





Notice

This manual provides information to dietary supplement¹ manufacturers who intend to participate in the United States Pharmacopeia Dietary Supplement Verification Program (USP DSVP or Program). Additional requirements and criteria that are not included in this manual, including those in the DSVP Mark Usage Manual, must be satisfied for participation. Prospective participants are advised to discuss these additional requirements with USP.

The Program is designed to assist participants in assuring their customers that the manufactured dietary supplement is produced in a facility that has implemented Good Manufacturing Practices (GMP) (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 on the participant's product labels 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.

¹ USP understands that the term *dietary supplement* in the US has different meanings in other countries. Non-US terms include: botanicals, herbals, herbal medicines, natural health products, and nutraceuticals.



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1. Overview

The USP Dietary Supplement Verification Program (USP DSVP or Program) is one of several public health programs of the United States Pharmacopeia (USP). Participation is voluntary and open to manufacturers of dietary supplements. The USP DSVP complements FDA's regulation of dietary supplements under the Dietary Supplement Health and Education Act of 1994 (DSHEA).

Based on the legal definition in the United States under DSHEA, USP considers a dietary supplement to mean a product intended to supplement the diet that bears or contains one or more of the following dietary ingredients: vitamins, minerals, amino acids, herbs or other botanicals, dietary substances used 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.

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 111 *Current Good Manufacturing Practice in Manufacturing, Packing, Labeling, or Holding Operations for Dietary Supplements*, and *USP-NF* general chapter <2750> *Manufacturing Practices for Dietary Supplements*.
- Product quality control and manufacturing evaluation of targeted dietary supplements submitted for verification, including review of product formulation, specifications, and stability; release data for compliance with specifications and label quantitative claims; review of critical quality attributes and the corresponding manufacturing control mechanisms of the critical quality attributes for the finished product; 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 Pharmacopoeia (ChP)*, and *Indian Pharmacopoeia (IP)* monographs, as applicable.
- Laboratory testing of targeted dietary supplement 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 supplements bearing the USP Verified Mark for continued compliance with Program requirements.
- Annual post-verification surveillance testing of targeted dietary supplements 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 supplements bearing the USP Verified Mark.

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

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



2. Requirements, Process and Submissions

Participants in the USP DSVP 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 Dietary Supplement Verification Program Manual for Participants*.
- Submit requested dietary supplement samples, data, and documentation.
- Subject their dietary supplements 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 supplements submitted for verification meet the requirements specified in *USP–NF*, *PhEur*, *BP*, *JP*, *ChP*, *IP*, and/or other compendia, where applicable.
- In the absence of *USP–NF* or other compendial standards for such dietary supplements, ensure that adequate data are submitted for substantiation of the quality of the dietary supplements, 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 supplement labeling 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 supplements and the corresponding requested information at <https://www.usp.org/verification-services/dietary-supplements-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 supplement(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 supplement(s) for which verification is sought, with the lot history dating back six months for lots of the dietary supplement(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 supplement(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. Product name (i.e., QA approved internal name) and product code
 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 and label the products submitted for verification
 5. Release testing documentation for packaging and labeling material lots used to package and label the product lots submitted for verification
 6. Master production and packaging batch record(s) for the product(s) submitted for verification
 7. Executed production and packaging batch records for the product lots submitted for verification
 8. Documentation associated with any in-process test results
 9. Finished product specifications for the dietary supplement(s) submitted for verification
 10. 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
 11. Dietary supplement in-process test results and supporting data when used for finished product release
 12. Data on reference standards used in release testing of the dietary supplement and documentation of the reference standard's suitability for use
 13. Test procedures used in release testing of the finished product



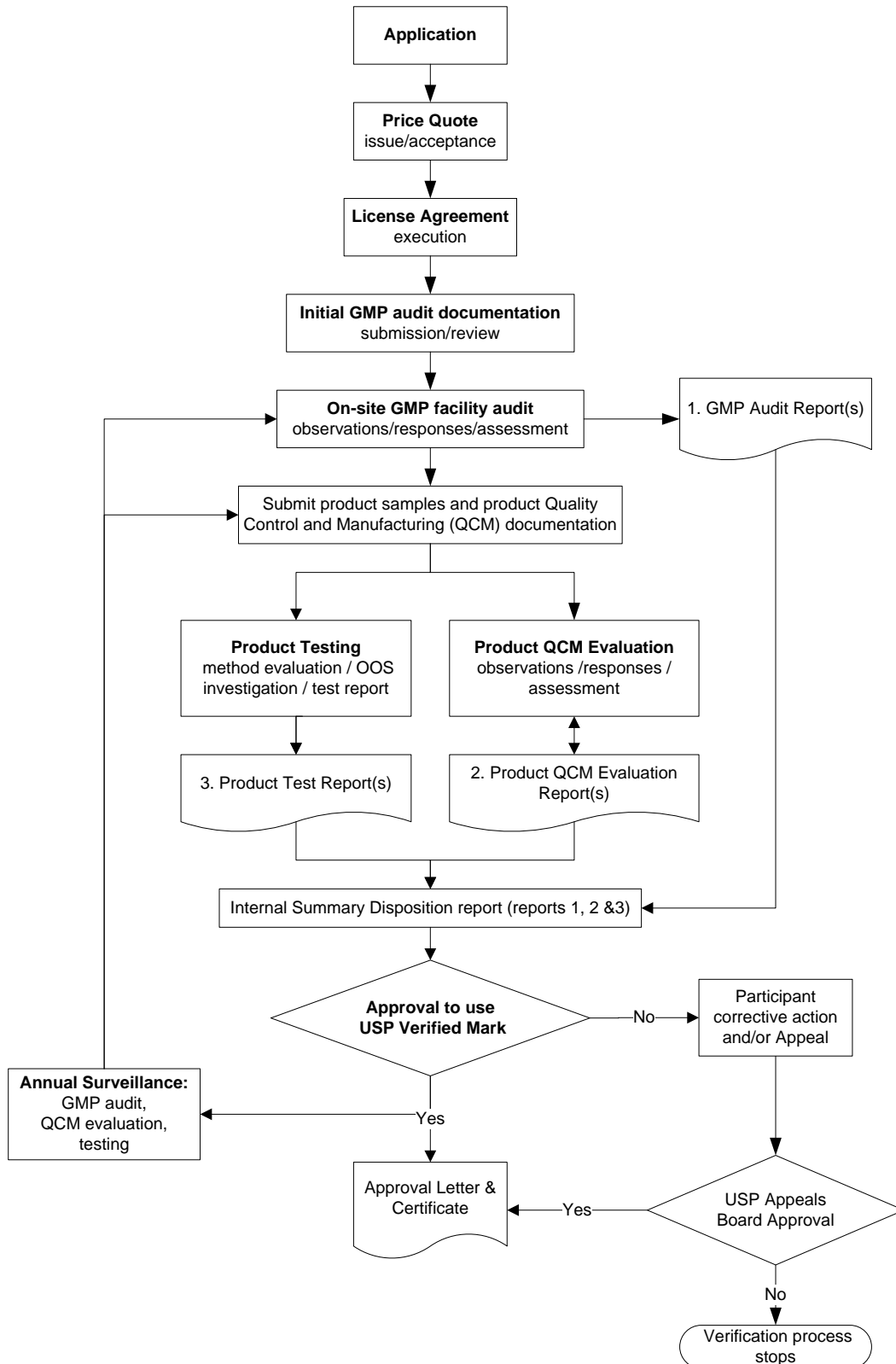
14. Verification data and report for compendial test procedures used for finished product release, per *USP–NF* general chapter <1226> *Verification of Compendial Procedures*
15. Validation protocol, data, and report for noncompendial (i.e., manufacturer) test procedures used for finished product release, per *USP–NF* general chapter <1225> *Validation of Compendial Procedures*
16. Report of results of stability studies used to support the expiry date of the dietary supplement [see ICH Q1A(R2) *Stability Testing of New Drug Substances and Products* for guidance].
 - 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 supplements for which verification is being sought, along with a copy of the specifications for each dietary supplement. USP staff will review the list of dietary supplements and their specifications to confirm that the dietary supplements are appropriate for inclusion in the Program. USP reserves the right to exclude dietary supplements from the Program if there are potential concerns with verification, e.g., safety-related issues, regulatory issues, or technical issues.

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

- Dietary supplements or dietary supplements containing ingredients that have monographs in the current *USP–NF*
- Dietary supplements or dietary supplements containing ingredients for which monographs have been proposed in *Pharmacopeial Forum (PF)*, or are in press for publication in *PF*
- Dietary supplements or dietary supplements containing ingredients for which monographs are under development by the appropriate USP Expert Committee
- Dietary supplements or dietary supplements containing ingredients for which no *USP–NF* monograph exists but for which there is a monograph in the *PhEur*, *BP*, *JP*, *ChP*, *IP*, or other pharmacopeia, as applicable
- Dietary supplements with 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
- Dietary Supplements with 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 supplements containing 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 supplement 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 supplement lot history (lot number, month of manufacture, manufacturing facility, and lot size) to USP for all lots of the dietary supplements 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 supplement(s) under consideration, the participant also submits the list of recalled lots, if any, in the past five years.



5. Product Categorization

Product categorization and sampling plans are important tools in the Program's verification strategy and are designed to ensure that an appropriate level of critical review is applied to all products being verified by USP.

If a participant is submitting one dietary supplement for verification, USP will select 3 lots of the dietary supplement to use for the verification process. The lots will be selected randomly based on the 6-month lot history for the dietary supplement and the availability of the dietary supplement lots for sampling. The lots will be selected from those that are manufactured at regular commercial scale. However, for a new product formulation, USP will accept pilot scale batches that are at least one-tenth the size of commercial scale batches for no more than 2 of the 3 lots selected for the verification process (i.e., at least 1 lot needs to be manufactured at regular commercial scale).

If a participant is submitting a large number of dietary supplements of a similar type, USP will attempt to categorize the dietary supplements into groups, evaluating several characteristics according to scientific and quality principles, following risk-based principles (e.g., level of quality management and scientific expertise), with the intent to cover all unique and variable aspects of the manufacture of dietary supplements, in order to manage the costs of product verification for the participant. The categorization can be based on a number of factors, including but not limited to the manufacturing site location and quality management system, product type (i.e., dosage form), and product classification based on the predominant dietary ingredients in the dietary supplement. The participant may provide an initial categorization of the dietary supplements for USP's review and consideration; however, USP at its sole discretion will make the determination regarding product categorization. The following table provides some examples of dietary supplement categorization based on the product type and classification of the dietary supplements (for illustrative purposes only, not intended to be an all inclusive list).

Characteristic	Dietary Supplement Categorization
Site of manufacture	Same site
Quality management system	Level of quality management and scientific expertise
Product type/ dosage form	Tablet and hard gelatin capsule Soft gelatin capsule Chewable gel (i.e., gummy) Liquid Powder



Characteristic	Dietary Supplement Categorization
Product classification	Single or multiple vitamin group Single or multiple mineral group Single or multiple amino acid group Multiple vitamins and minerals group Botanicals (same genus and species) group Single probiotic (same species and strain) group Multiple probiotic group Single other dietary substances group Multiple other dietary substances (case by case)

Note that participants in the Program are encouraged to consider a single product submission for their initial product verification to help them gain an understanding of the product verification process and quality expectations. By applying the learnings from a prior successful product verification experience, the participant may be able to preemptively address quality issues of known concern to USP in future product submissions, thereby reducing the time and costs for future product verifications.

The number of dietary supplements selected from each product group for initial verification will be determined based on the square-root of N plus one ($\sqrt{N + 1}$), where N is the number of dietary supplements in the group, but not less than 3 will be selected per group. If the number of dietary supplements in the group is less than 3, then all of the dietary supplements in the group will be selected for initial verification. Within each product group, USP will select a minimum of 3 lots of dietary supplement for initial verification. Dietary supplements 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 section 8.



6. Initial GMP Quality Systems Facility Audit

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 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 (SOPs) 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 ingredients (i.e., components), in-process material, 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 material ingredients, 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, in-process material, 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

Major or minor nonconformities observed during review of the initial GMP quality systems facility audit documentation will be addressed during the on-site audit, and if necessary, cited in the on-site audit report. If USP staff 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, 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 111 *Current Good Manufacturing Practice in Manufacturing, Packing, Labeling, or Holding Operations for Dietary Supplements*
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 supplements, 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 supplements
- Materials System, which includes the measures and activities used to control the raw materials, in-process material, 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 supplements 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 supplements
- Laboratory Control System, which includes the activities and controls related to testing, raw materials, in-process material, and finished product for conformance to specifications, including laboratory procedures, analytical methods development, validation and/or verification, and dietary supplement stability studies

Auditors will apply the following criteria:

Organization/Personnel

- Dedicated quality assurance/quality control department
- Training program for the competency of all employees, including hygiene training

Quality Assurance System

- System to ensure dietary supplement 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 (i.e., IQ, OQ, PQ and system validation)
- 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 material ingredients, manufactured in-process material, and finished dietary supplements
- System of material reconciliation

Validation

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

Deviations

- Maintenance of deviation logs
- Policy with time frame for the disposition of deviations
- Procedure 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 supplement stability
- Testing within defined time frames
- Formal program for resolution of discrepancies in testing
- Data to support shelf-life (i.e., expiry) date of dietary supplements 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 supplement. 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 supplement 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 supplement is verified.



8. Submission of Product Samples and Documentation

Submission of Product Samples

Sample aliquots from the selected dietary supplement 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 supplement 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 and certificate of analyses.

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

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

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).

Full Initial QCM Documentation:

1. Specifications for raw materials, packaging, and finished product
 - a. Raw material specifications for raw materials used to prepare finished products undergoing verification
 - b. Release specifications for bulk product (if applicable)
 - c. Packaging specifications for bulk product (if applicable)
 - d. Packaging and labeling specifications for primary and/or secondary packaging used for finished products
 - e. Release and shelf-life specification for finished products



2. Test methods and reference standards used for testing of raw materials used to prepare finished products and testing of finished products undergoing verification
 - a. Written test method/procedure
 - b. Data demonstrating suitability of method for intended use (e.g., method validation/verification protocol and method validation/verification data/report)
 - c. Reference materials used for testing
 - i. Description (name, source, quality) of the standard (if not included in the written method)
 - ii. Data to support the suitability of standard for intended use
3. Release documentation for the lots of raw materials
 - a. QC laboratory release form and test results for raw materials (CoA, if applicable)
 - b. Certificate of Analysis (CoA) from the supplier
4. Release Documentation for the finished product lots
 - a. QC laboratory release form for the finished product (CoA, if applicable)
 - b. Test results and the corresponding raw data (i.e., laboratory notebook pages, spectra, chromatograms, etc.)
5. Stability data for each unique packaging configuration for the finished products undergoing verification
 - a. Stability protocol
 - b. Test results summary to support the marketed shelf-life
6. Master formula and manufacturing batch production record
 - a. Master manufacturing batch records, including any premixes and subassemblies
 - b. Approval signatures and date(s) for master batch records
7. Master packaging batch records
 - a. Master packaging batch records
 - b. Master label copy
 - c. Approval signatures/dates for master packaging records and label
8. Executed manufacturing batch production records
 - a. Executed manufacturing batch records, including any premixes and subassemblies
 - b. In- process test data/results and percent yield calculations/results



- c. Shelf-life calculation
 - d. Sample bulk label and label reconciliation
 - e. Final QA approval signature/date of bulk lots
9. Executed packaging batch records
- a. Executed packaging batch records
 - b. Incoming inspection and release of labels and packaging materials
 - c. Sample label and label reconciliation
 - d. Final QA approval signature/date of finished packaged lots

Limited Initial QCM Documentation:

1. Specifications for any unique raw material, any unique packaging configuration, labeling and finished product
 - a. Raw material specifications for any unique raw materials, i.e., materials not common to other products in the group
 - b. Packaging specifications for any unique primary and/or secondary packaging configurations used for finished products not common to other products in the group
 - c. Labeling specification
 - d. Release and shelf-life specification for finished products
2. Test methods and reference standards not common to other products in the group used for testing of raw material used to prepare finished products and testing of finished products undergoing verification
 - a. Written test method/procedure
 - b. Data demonstrating suitability of method for intended use (e.g., method validation/verification protocol and method validation/verification data/report)
 - c. Reference materials used for testing
 - i. Description (name, source, quality) of the standard (if not included in the written method)
 - ii. Data to support the suitability of standard for intended use
3. Release documentation for the most current lot of unique raw materials, i.e., raw materials not common to other products in the group
 - a. QC laboratory release form and test results for raw materials (CoA, if applicable)
 - b. Certificate of Analysis (CoA) from the supplier



4. Stability data for each unique packaging configuration for the finished products undergoing verification
 - a. Stability protocol
 - b. Test results summary to support the marketed shelf-life
5. Master formula and manufacturing batch production record
 - a. Master manufacturing batch records, including any premixes and subassemblies
 - b. Approval signatures and date(s) for master batch records
6. Master packaging batch records
 - a. Master packaging batch records
 - b. Master label copy
 - c. Approval signatures/dates for master packaging records and label

Limited Surveillance QCM Documentation:

1. Release Documentation for the finished product lots
 - a. QC laboratory release form for the finished product (CoA, if applicable)
 - b. Test results and the corresponding raw data (i.e., laboratory notebook pages, spectra, chromatograms, etc.)
2. Current Stability data for each unique packaging configuration for the finished products undergoing verification
 - a. Stability protocol
 - b. Test results summary to support the marketed shelf-life
3. Executed manufacturing batch production records
 - a. Executed manufacturing batch records, including any premixes and subassemblies
 - b. In- process test data/results and percent yield calculations/results
 - c. Shelf-life calculation
 - d. Sample bulk label and label reconciliation
 - e. Final QA approval signature/date of bulk lots
4. Executed packaging batch records
 - a. Executed packaging batch records
 - b. Incoming inspection and release of labels and packaging materials
 - c. Sample label and label reconciliation
 - d. Final QA approval signature/date of finished packaged lots



For limited surveillance QCM documentation, 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.

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

Common Technical Document (CTD): Note that the requested QCM documentation information may be submitted in the format of the Chemistry, Manufacturing, and Controls (CMC) Documentation following the format of the quality section of the ICH 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.

Sampling Plans: Single Product versus Product Group Submissions

Product categorization and sampling plans are important tools in USP's verification strategy and are designed to ensure that an appropriate level of critical review is applied to all products being evaluated by USP prior to awarding the USP Verified Mark. If a participant is submitting a large number of dietary supplements of a similar type, USP will attempt to categorize the dietary supplements into groups, as described in section 5.

The bulk finished product constitutes the primary item under verification. The same bulk product item may be packaged in a variety of different finished package configurations, e.g., PET bottles, HDPE bottles, blister packs and/or pouches, with various product counts for each possible configuration or stock keeping unit (sku). USP will attempt to sample product from each available package configuration; however, if product samples in some package configurations are not available for sampling, the suitability of these configurations will be assessed through additional documentation reviews.

For all products submitted for USP verification, master documentation describing the manufacturing and quality controls of each product submitted for USP verification is evaluated (i.e., 100% review of master documentation is required). Additionally, representative samples of randomly selected product lots are tested and their corresponding executed QCM documentation are reviewed in order to confirm conformance of the products to the applicable product quality standards and compliance by the participant to the relevant manufacturing and quality control systems. The sampling plan for product samples and documentation will vary for a single product versus a product group submission, as described in the following two tables.



Sampling Plan for Single Product Submission

Item	Sampling Strategy
Product Lot Selection (Laboratory Testing)	A minimum of three (3) unique lots of packaged finished product, representing at least three (3) unique bulk product lots, will be selected at random by USP for testing, from the participant's available inventory. When feasible, at least one (1) lot representing each finished product package configuration will be sampled.
Product Documentation Selection (QCM Documentation Review)	<p><u>Full Initial QCM Documentation Review:</u> The complete QCM documentation and records for the same lots, which were sampled for testing by USP (see above), will be required for evaluation.</p> <p><u>Limited Document Review / Additional Documents Required:</u> Generally, limited documentation review is not applicable to single product submissions. If USP is unable to sample all finished product packaging configurations, then additional documentation addressing the unique packaging operations, packaging controls and product stability in the unique packaging configuration(s) will be required and will be handled through a limited documentation review approach.</p>

Sampling Plan for Product Group Submission

Item	Sampling Strategy
Product Lot Selection (Laboratory Testing)	<p>For product groups consisting of two (2) different bulk product codes, both products will be sampled. Typically, two (2) unique lots of packaged finished product, each representing a unique bulk lot number, will be selected at random by USP for testing from each bulk product code (i.e., a minimum of four (4) lots for testing).</p> <p>For product groups consisting of three (3) or more different bulk product codes, a minimum of half of the products within the product group submission must be tested as part of initial verification.^{a, b} The specific products (bulks) requiring testing will be selected by USP using a risk based approach. Specific lots of the products chosen for testing will be selected at random by USP from the participant's available inventory.</p>



Item	Sampling Strategy
Product Documentation Selection (QCM Documentation Review)	<p><u>Full Initial QCM Documentation Review:</u> Within each product group, the complete QCM records for the square root of n plus one [i.e., $\sqrt{n} + 1$] lots, where n is the total number of products in the group, will be required for evaluation.^β The specific products/lots requiring full QCM review will be selected by USP from the lots undergoing laboratory testing (see above).</p> <p><u>Limited Document Review / Additional Documents Required:</u> USP must review the critical QCM documents for each product undergoing concurrent verification as part of the product group (i.e., inclusive of the products which were not sampled or subject to full QCM documentation review). The critical QCM documents include the following:</p> <ol style="list-style-type: none"> a. Finished product release specification b. Finished product labels c. Master formula & master batch record d. Assay test method(s) and method validation(s) for tests not common to other products in the group e. Raw material release specifications and supplier specifications (or CoAs) for any unique raw materials, i.e., materials not common to other products in the group f. Stability reports supporting the proposed shelf-life for each unique packaging configuration

^α The other products in the group, i.e., the half not sampled in the initial round, will undergo testing during the first annual market surveillance testing of the product group, which will occur in the first year after the approval to use the USP Verified Mark has been granted.

^β As a minimum, at least four (4) product lots will be subject to testing and to full QCM documentation review.

Technical Feasibility Review

For dietary supplements with no compendial monograph, USP staff will conduct an initial technical feasibility review of the participant’s dietary supplement specification and test methods to determine whether the information supports the ability to control the quality of the dietary supplement 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 dietary supplement. 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 supplement(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 supplement(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 supplements accepted into the Program.

Quality Control Documentation:

USP will determine whether the specifications (tests, analytical procedures, and acceptance criteria) provided are sufficient to demonstrate consistent and appropriate dietary supplement quality. USP will review specifications relating to raw materials, in-process materials, final dietary supplements, packaging and labeling materials, reference standard 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, In-Process Material, and Final Dietary Supplements: For raw material and dietary supplements 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). If a raw material or dietary supplement does not comply with the requirements specified in a monograph, USP will request submission of data as explanation for the discrepancy. USP Verification staff will evaluate the data for acceptance and the firm’s justification.

For dietary supplements 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 supplements, 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)
- Impurities
 - Elemental impurities (see *USP–NF* general chapters <2232> *Elemental Contaminants in Dietary Supplements* and <233> *Elemental Impurities Procedures*)
 - Residual solvents (see *USP–NF* general chapter <467> *Residual Solvents*)
 - Known toxic impurities (see *USP–NF* general chapter <561> *Articles of Botanical Origins – Test for Aflatoxins, Pesticide Residue Analysis*)
 - Microbial contaminants (see *USP–NF* general chapter <2023> *Microbiological Attributes of Nonsterile Nutritional and Dietary Supplements*)



- Specific tests (e.g., see *USP-NF* general chapter <401> *Fats and Fixed Oils - Peroxide Value, Anisidine Value*)
- Performance tests (see *USP-NF* general chapter <2040> *Disintegration and Dissolution of Dietary Supplements*)

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*.

For in-process material, USP will verify that the specifications provided by the participant are adequate to ensure that the dietary supplement meets its specification.

For in-process material purchased from contract manufacturers, participants must have a supplier qualification program in place. In general, USP will not subject these in-process material to additional testing except when the penultimate in-process material 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 supplement (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*, other pharmacopeias, and standards on labels or labeling must be completely accurate. Labeling must comply with all applicable regulatory and compendial labeling requirements.

The current edition of *Herbs of Commerce*, published by the American Herbal Products Association (AHPA), should be consulted regarding the proper Latin binomial and Standardized Common Name for each botanical species.

Note that in terms of the relationship between marker compounds and label claims, federal regulations 21 CFR part 101.9(g)(3), 101.9(g)(4), and 101.36(f)(1) require that products be truthfully labeled with respect to their contents. The FDA has established two different minimum levels that label claims must meet depending on the type of ingredient. Fortified or fabricated (Class I) nutrients, whose content has been controlled in some fashion must meet 100% of label claim. Naturally occurring (Class II) nutrients, whose constituents occur naturally in an ingredient and whose level is not



controlled must meet at least 80% of label claim. For DSVP, a botanical or “other dietary supplement” extract with declared chemical marker constituents on the label is considered a Class I (standardized) nutrient, whereas a powdered botanical or “other” dietary supplement is considered a Class II (nonstandardized) nutrient. In both cases, the rule applies to the product throughout its shelf life.

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 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.

Method Verification: If the analytical procedure is found in an official compendium, such as *USP–NF*, *AOAC International Official Methods of Analysis (OMA)*, *AOAC International Peer Verified Method (PVM)*, there is no need for a complete validation report. In this case, the suitability of the test procedure for testing the specific dietary supplement must be supported by analytical data; the data should check the accuracy and precision of the analyte determination and lack of interference from other components/excipients with the analyte. See *USP–NF* general chapter <1226> *Verification of Compendial 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 supplement 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 supplement’s quality. Real-time or long term stability studies will be used for review. If data from real-time or long term



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.

For new dietary supplements containing new dietary ingredients of unknown stability, the Program allows acceptable 3-month and 6-month accelerated (at $40\text{ }^{\circ}\text{C} \pm 2\text{ }^{\circ}\text{C}$ / $75\% \text{ RH} \pm 5\% \text{ RH}$) stability studies for a minimum of 1 batch (although a minimum of 3 batches is preferred in cases in which data shows significant degradation) to temporarily support a shelf life of 2 years and 3 years, respectively, with a commitment to provide on-going real-time (under controlled labeled storage conditions) or long term (at $25\text{ }^{\circ}\text{C} \pm 2\text{ }^{\circ}\text{C}$ / $60\% \text{ RH} \pm 5\% \text{ RH}$) at the end of the declared shelf-life period. USP prefers that commercially manufactured batches be used; however, a pilot batch that is of suitable size and that uses equipment consistent with what will be used in commercial manufacturing can also be used.

For new dietary supplements containing new dietary ingredients of unknown stability that are not conducive to accelerated stability studies, the Program allows acceptable 3-month intermediate (at $30\text{ }^{\circ}\text{C} \pm 2\text{ }^{\circ}\text{C}$ / $65\% \text{ RH} \pm 5\% \text{ RH}$) stability studies for at least 1 batch to temporarily support a shelf life of 1.5 years, with a commitment to provide on-going real-time (under controlled labeled storage conditions) or long term (at $25\text{ }^{\circ}\text{C} \pm 2\text{ }^{\circ}\text{C}$ / $60\% \text{ RH} \pm 5\% \text{ RH}$) at the end of the declared shelf-life period.

For existing commercial products, comparing test data from suitably retained samples, which have been manufactured under the current quality system and have been stored under controlled labeled storage conditions, and have been tested for necessary stability indicating quality attributes against initial release data may be sufficient to support the product's shelf-life period.

If the stability data shows little degradation and variability such that it is apparent from looking at the data that the requested shelf-life period is achievable, formal statistical analysis is unnecessary. However, if the stability data shows significant degradation, the nature of it will determine how the data should be transformed for regression analysis (e.g., linear, quadratic, or cubic function), which may be uncertain if only limited data of 1 batch is used to support the shelf-life period. Limited extrapolation of the data beyond the observed range to extend the shelf-life period can be undertaken if justified.

After initial certification of a product, supplemental stability data shall be reviewed to ensure that the data support the declared shelf life of the product.



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 supplement 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* (which contains information useful to articles other than excipients, including raw materials and finished products). 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
- 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 in-process steps involved in manufacturing

Executed Manufacturing Batch Records (EMBRs): The documentation submitted must include the executed batch records for the lots that USP has selected for testing. 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., mixers, tablet presses, encapsulators) used
- Specific identification of each batch, including weights, measures, and batch number of raw materials, in-process material, 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 supplement
- 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 supplement 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 supplement samples submitted by the participant will add useful data, USP will review any additional supplied procedures and/or analytical test results.

The dietary supplement 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. (See section 10 for further details on testing of product samples.)

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 1 critical 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 supplement. 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 supplement 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 supplement is verified.



10. Testing of Product Samples

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

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

USP will coordinate testing of dietary supplement samples in USP laboratories and/or by one or more approved contract laboratories. A single analysis will be performed for each dietary supplement test. Test data will then be evaluated for accuracy and to determine if the dietary supplement 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 suspected, 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 supplement 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 supplement 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 supplement. Action Level 1 critical issues must be adequately resolved before the verification process can continue for the dietary supplement and may require the manufacturing site be re-audited and/or the dietary supplement 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 supplement 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 supplement quality attribute or criteria through a major change to the dietary supplement. Action Level 2 major issues must be adequately resolved before a dietary supplement 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 supplement quality attributes or criteria. Action Level 3 issues may be resolved by supplying requested information or by making requested improvements to the dietary supplement quality attributes or criteria through a minor change to the dietary supplement. 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 supplement 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 supplement verification.



12. Product Approval Process

Satisfactory completion of the items listed below for each dietary supplement or dietary supplement 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 supplement samples for conformance to specifications (section 10)

For each dietary supplement or dietary supplement group that successfully completes the verification program requirements, USP will issue an approval letter. The approval letter will specify which of the participant's dietary supplements 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 supplement. 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 supplement 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 supplements 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 supplement-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 supplement-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, a participant might make changes to a product's specifications, process control data, raw material source, manufacturing site change, testing, or any other criteria deemed by the participant to be essential or significant to product quality.

Major changes must be reported in writing to USP upon implementation but prior to commercialization. Minor changes must be reported in the Annual Product Review (APR) report as part of post-verification surveillance activities (see section 15). A list of the products that are impacted by such changes, along with the rationale for the changes, needs to be clearly indicated.

During the re-evaluation and/or re-testing period, the participant may continue to use the USP Verified Mark on product batches manufactured with the change(s) in accordance with approved specifications, so long as sufficient supporting documentation for the change has been provided to USP. The participant must provide batch details that include batch/lot number, date of manufacture, and date of expiry of products of the first batch manufactured under such changed conditions.

- **Major Site Changes:** Major site changes include, but are not limited to, the following: (1) a move to a site that has not been audited and found to be acceptable by USP-DSVP; (2) the addition of a new manufacturing operation, such as manufacture of a liquid line where only tablet and/or capsules have been manufactured previously, for manufacturing USP verified products; and (3) the manufacture of a USP verified product from a product group (product type and classification) that the site has not been approved to manufacture.
- **Major Changes to Equipment:** A change to equipment different in design and operating principle.
- **Major Changes in Composition and Components:** Major changes in composition and components include, but are not limited to, the following: (1) addition of a new product to a USP-DSVP verified product group; (2) the addition of a new dietary ingredient to a formulation; (3) changes to excipient amounts that are likely to have a detectable impact on formulation quality and performance.
- **Major Process Changes:** Changes to the type of process used in the manufacturing of the product, such as change from wet granulation to direct compression of dry product.



- **Major Changes to Specification:** Major changes to specifications include, but are not limited to, the following: (1) the assay range or some other significant test parameter is broadened by a significant amount, usually as a result of a formulation change; and (2) a change in the analytical methodology employed for a given test.
- **Major Change to Label:** Any change to the supplement facts panel, the ingredient list, the order of ingredients listed on the label, or claims on the label.
- **Minor Changes:** All other changes not specified.

Documentation

The firm should document the evaluation of changes to the dietary supplement, regardless of the level of change. The report should indicate the basis for evaluating the effect of the change on the dietary supplement, 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 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 should be communicated by the participant to USP in the APR report (see section 15); change notification prior to implementation is not required.

Upon receipt of information regarding changes, USP will review the information in the change notification and determine whether it concurs with the participant's rating of the risk level, i.e., whether the changes are major or minor. 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 supplement to be re-evaluated or the dietary supplement retested.

If re-evaluation and/or retesting is not required, the participant may continue to use the USP Verified Mark in accordance with licensed terms. If re-evaluation and/or retesting 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 and/or retesting has been completed.



The participant may appeal the decision to require re-evaluation and/or retesting under the appeals 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 and/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, 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 and if applicable, any responses to observations 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 supplement, the participant must provide USP with an Annual Product Review (APR) report. The APR report for each verified dietary supplement (or group of dietary supplements) 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 3 months 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 supplements manufactured during the preceding year
- List of deviations recorded in these dietary supplements
- List of all quality-related OOS results/investigations
- List of customer complaints/recalls
- List of all changes (major and minor)
- Progress on corrective actions against observations noted during product QCM evaluation
- Updated current stability data

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 supplement, USP will perform at a minimum an annual evaluation of the dietary supplement (or product group of dietary supplements) to ensure that it (they) continue(s) to meet the Program criteria. When many dietary supplements in a product group have been submitted for verification, the dietary supplements evaluated during post-verification surveillance typically will be those that did not undergo full product QCM evaluation and/or product testing in previous year.

USP will perform "off-the-shelf" evaluation of dietary supplements. Nation-wide sampling will be conducted as appropriate. The participant may be contacted to determine the outlets through which the product is being distributed. USP-designated representatives will be asked to select specific products from various marketing locations and ship the products to USP. Under rare circumstances when USP has difficulty locating a sufficient number of product samples of the same lot number needed for product testing, the participant may be required to submit samples from one of their distribution centers. Alternatively, USP auditors may collect samples during the annual on-site GMP quality systems facility audit and ship them to USP.



The participant will be required to submit corresponding limited surveillance QCM documentation (see section 8) 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. USP will conduct product QCM evaluation and report its findings in a product QCM evaluation report per the reporting and corrective action procedure described in section 9.

USP will test the samples it receives in accordance with the compendial and/or participant's specification per the steps outlined in section 10. USP also may request further documentation based on the dietary supplement 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 supplement contains known contaminants.



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 supplement 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 supplement bearing the USP Verified Mark if critical dietary supplement nonconformities are detected. Dietary supplement nonconformities are considered critical if

- There is a reasonable probability that the use of, or exposure to, the dietary supplement 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 supplement 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 supplement problem. USP will then affirm or reverse its recommendation to recall the dietary supplement. 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 supplement. 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 supplement nonconformities, which involve a major deviation from dietary supplement 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 supplement. 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 supplement.

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 (i.e., USP 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 supplement 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 Pharmacopoeia 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 and drug product 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 supplement 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).

Component: A component means any substance intended for use in the manufacture of a dietary supplement, including those that may not appear in the finished batch of the dietary supplement. Component includes dietary ingredients and other ingredients.

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

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.

Expiry Date: The end of the time interval during which the dietary supplement must conform to applicable specifications when stored under labeled conditions. The expiry date should be supported by stability data and should be indicated on the dietary supplement label and exterior commercial packaging. Expiry date is also referred to as shelf-life and expiration date.

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 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).

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.

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.

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 supplement 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 Dietary Supplement Verification Program 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 supplement 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 supplement 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 supplements 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 intended for use in the manufacture of a dietary supplement. A raw material is also referred to as a component.

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



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 Supplement(s): Dietary supplement(s) chosen for evaluation to represent a group of dietary supplements that have been grouped based on (but not limited to) their product type (i.e., dosage form), product characteristics (i.e., predominant dietary ingredients present in the dietary supplement), site of manufacturing, 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 supplement, based on the quantity of raw materials or packaging to be used, in the absence of any loss or error in actual production.

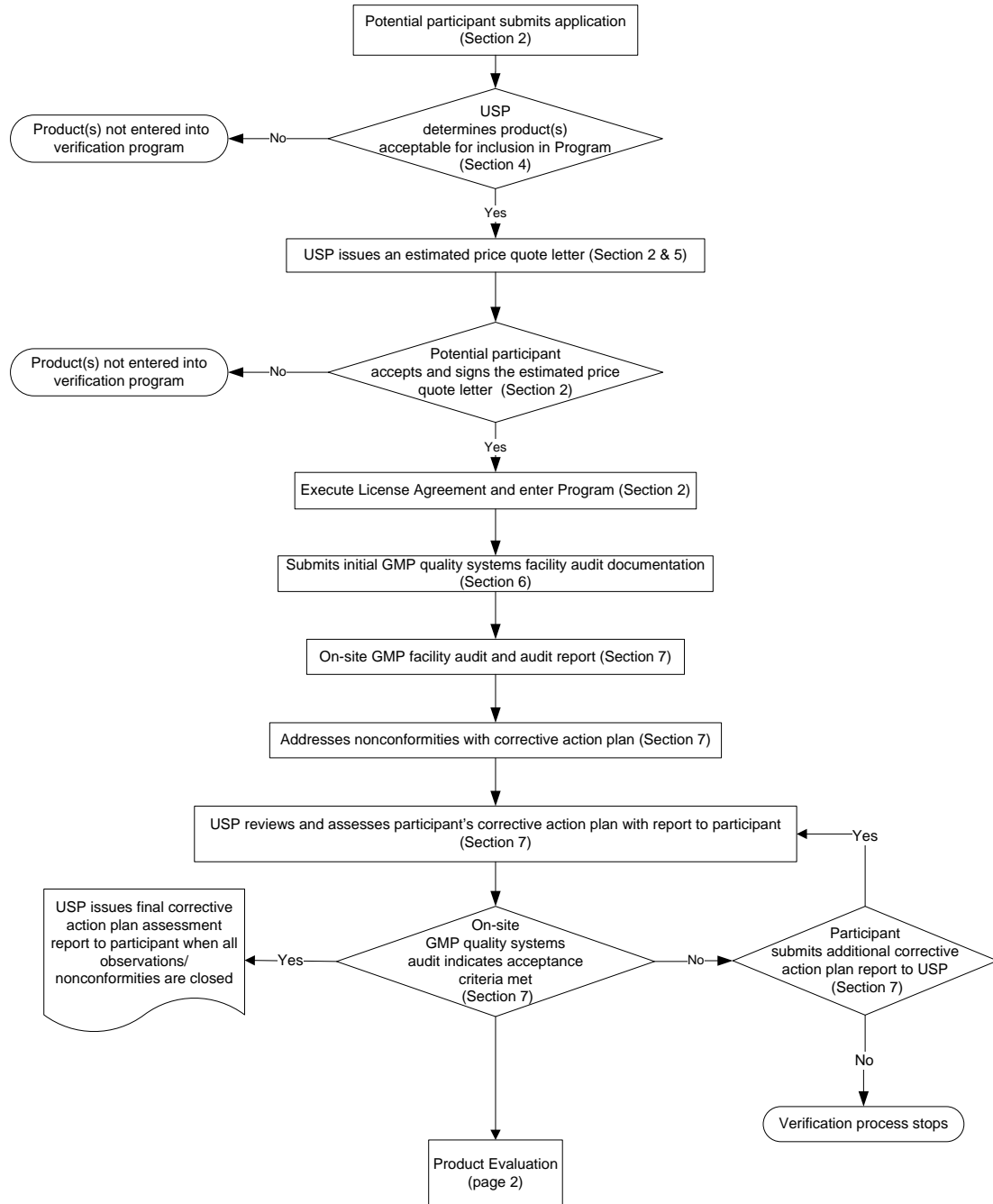
United States Pharmacopeia–National Formulary (USP–NF): The current official volume of the *United States Pharmacopeia–National Formulary*, including its supplements. It contains official article (substance and product) monographs, as defined in the *General Notices of USP–NF*, as well as General Tests 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.

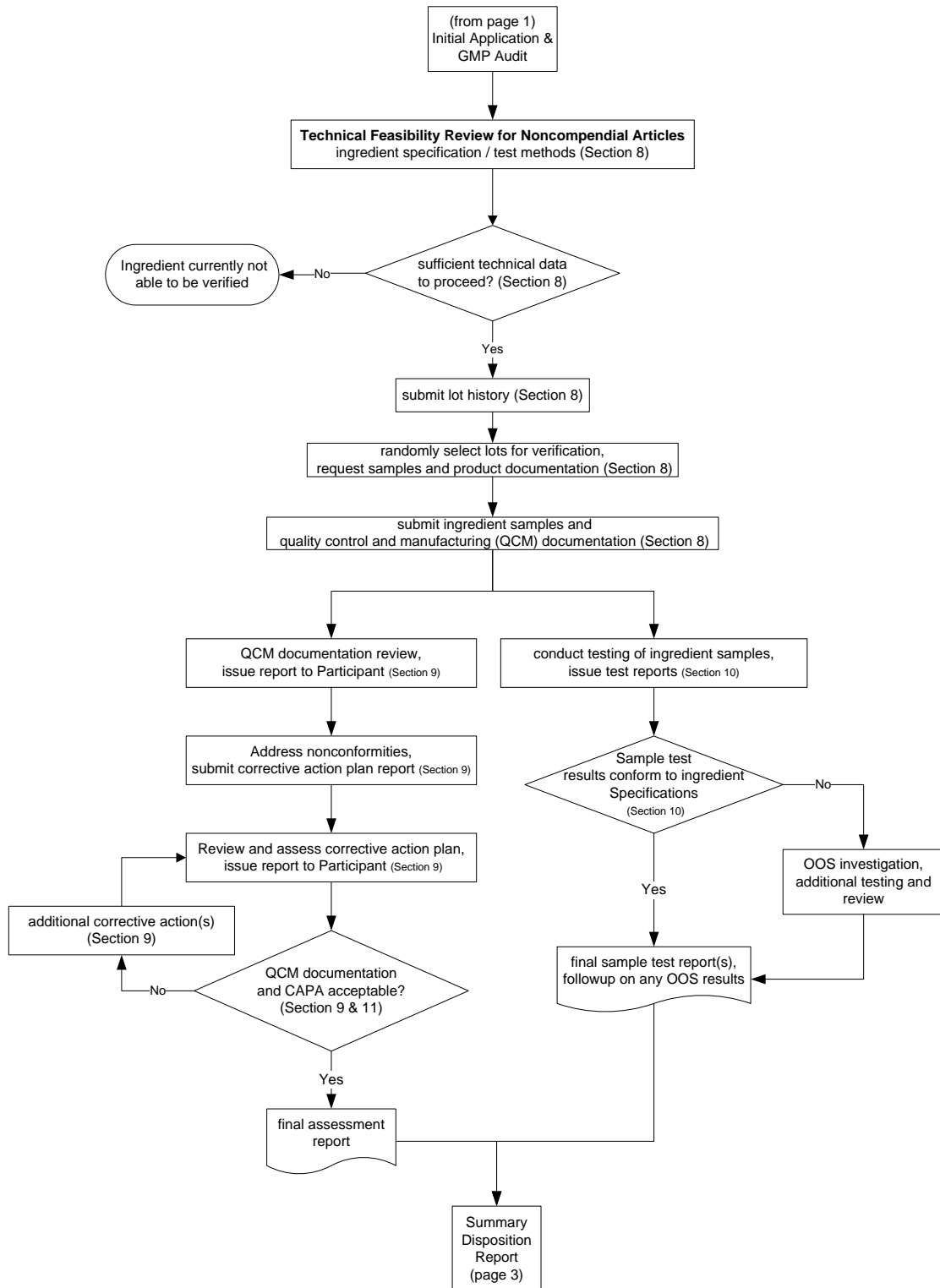
USP Reference Standard: Substances selected for their high purity, critical characteristics, and suitability for the intended purpose. They are used to test for compliance with *USP–NF* requirements, to demonstrate identity, strength, quality, and purity of official articles.

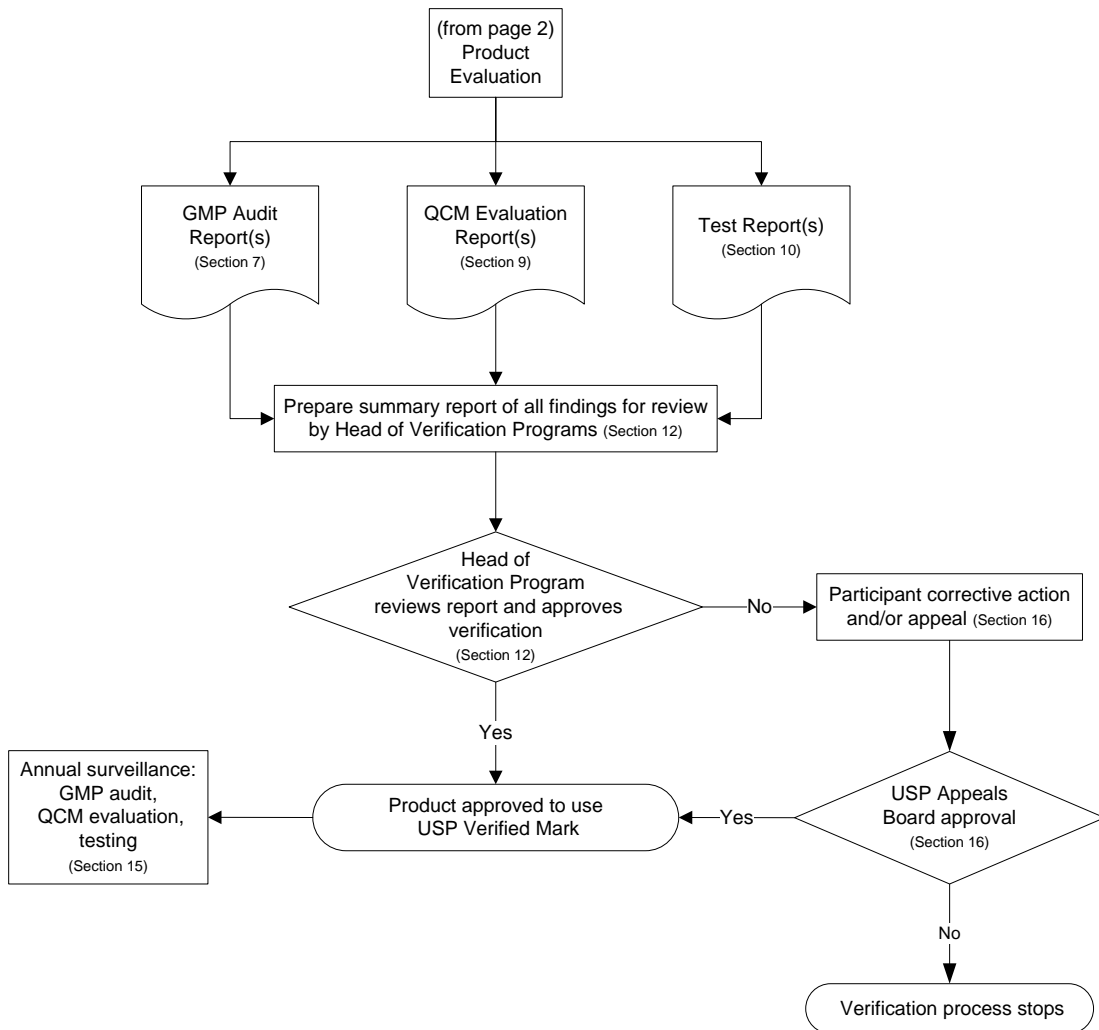


18. Appendix

A. Detailed Process Flowcharts









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 raw material ingredients, in-process material, 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, in-process material 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 Dietary Supplement Verification Program

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 - Excipient Manufacturer

Audit Standards: FDA 21 CFR Part 111 *Current Good Manufacturing Practice in Manufacturing, Packing, Labeling, or Holding Operations for Dietary Supplements*, and USP-NF general chapter <2750> *Manufacturing Practices for Dietary Supplements*.

Audit Duration: {Typically three (3) days}

Scope: Full Audit for USP Dietary Supplement Verification Program



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, in-process material, 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 supplements

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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