

NOTICE

This manual provides information to excipient manufacturers who intend to participate in the United States Pharmacopeia's Excipient Verification Program (USP EVP or Program).

The Program is designed to assist participants in assuring their customers – drug product manufacturers and others – that the manufactured excipient is produced in accordance with Good Manufacturing Practices (as defined in this manual) and the participant's other quality controls and systems comply with the ingredient label and meet other Program requirements. USP considers this to be a cooperative effort between USP and participants. Participants who meet the requirements of this Program will receive permission to use a special USP Certification Mark for use in conjunction with a certificate of analysis or similar document. Barring safety concerns or other special circumstances (see section 17, "Appeals"), USP maintains the confidentiality of information gained through the verification process in accordance with the provisions of the Program License Agreement, provided separately.

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1. OVERVIEW

The USP's Excipient Verification Program (USP EVP or Program) is one of several public health programs of the United States Pharmacopeia (USP). Participation is voluntary and open to manufacturers of excipients for use in drug products (medicines).

The Program includes a general conformity assessment as follows:

- Evaluation of participants' quality systems through audit of each manufacturing site for compliance with Good Manufacturing Practices (i.e., USP General Chapter <1078> *Good Manufacturing Practices for Bulk Pharmaceutical Excipients*; the Joint International Pharmaceutical Excipients Council and Pharmaceutical Quality Group (IPEC-PQG) *Good Manufacturing Practices Guide for Pharmaceutical Excipients*, and the World Health Organization (WHO) Technical Report Series, No. 885, 1999, Annex 5: *Good manufacturing practices: supplementary guidelines for the manufacture of pharmaceutical excipients*)
- Review of chemistry, manufacturing, and controls documentation for targeted excipients submitted for verification, including review of characterization, stability, and/or release data for compliance with labeling and certificate of analysis claims as well as compliance with *United States Pharmacopeia and the National Formulary (USP–NF)*, European Pharmacopoeia (EP), British Pharmacopoeia (BP), Japanese Pharmacopoeia (JP) monographs, as applicable
- Laboratory testing of targeted excipient samples from selected lots for compliance with labeling or certificate of analysis claims and Program requirements
- Grant of the USP Certification Mark upon full satisfaction of Program requirements
- Post-verification surveillance testing of targeted excipients bearing the USP Certification Mark
- Periodic re-verification
- Reporting by participants of changes to the chemistry, manufacturing, and controls for excipients bearing the USP Certification Mark

The use of the distinctive USP Certification Mark is granted for excipients that successfully meet Program requirements. The mark indicates the verification of excipient quality by a trusted and established authority – USP. It provides assurance that

- The participant has established and is following a quality system that helps ensure that the excipient evaluated meets its labeling or certificate of analysis claim for identification, strength, purity, and quality, and is consistent in quality from batch to batch.
- The participant follows accepted manufacturing practices in producing the subject excipient.

- The tested excipient samples meet requirements for acceptable limits of contamination and impurities.

2 | CRITERIA FOR PARTICIPATION

Participants in the USP EVP must do the following:

- Complete and comply with all provisions of the Program License Agreement.
- Submit requested data and documentation.
- Subject their excipients 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 excipients submitted for review meet the requirements specified in *USP-NF*, EP, BP and/or JP where applicable. In the absence of *USP-NF*, EP, BP and/or JP standards for such excipients, ensure that adequate data are submitted for substantiation of the quality of the excipient(s) and that there are analytical procedures in place to perform the necessary tests.
- Provide recall history of submitted excipients, dating back five years, as applicable.
- Provide stability data to support the claimed retest date of the excipient.
- Pay all fees required by USP agreements or by documents executed between the participant and USP.
- Act in compliance with the *USP Pharmaceutical Ingredient Verification Program Mark Usage Manual*, which provides (a) rules regarding the placement of the mark on excipient labeling and certificates of analysis, and (b) guidelines for advertising.

3. **REQUIRED PROCESS AND SUBMISSIONS**

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.

Participants that wish to participate in the Program shall:

- Submit application with selected excipient list and excipient information at <http://www.usp.org/USPVerified/pharmaceuticalIngredients/join.html>
- Appoint a duly authorized representative to execute a License Agreement.
- Provide the following financial and legal information:
 - Description of any litigation related to the excipient(s) for which verification is sought, and a description of any pending or threatened litigation against the participant
 - Description of general liability and product liability insurance, including limits expressed in U.S. dollars
 - Results of audits performed by government regulatory agencies during the past three years, including the United States Food and Drug Administration (FDA)
 - List of countries in which the participant is licensed to do business
 - Copies of all relevant permits, approvals, and certificates of insurance, as required by the Program License Agreement
- Provide the list of excipients for which verification is sought, with lot history dating back six months or fifteen batches, whichever comes first, of the excipient(s) manufactured under the current quality system.
- Provide USP with representative sample aliquots of the excipients, as specified by USP staff.
- Submit the following Chemistry, Manufacturing, and Controls (CMC) documentation as described in this manual (see section 19, "Forms and Checklists), as requested by USP staff and/or have available for review during the on-site audit, including but not limited to:

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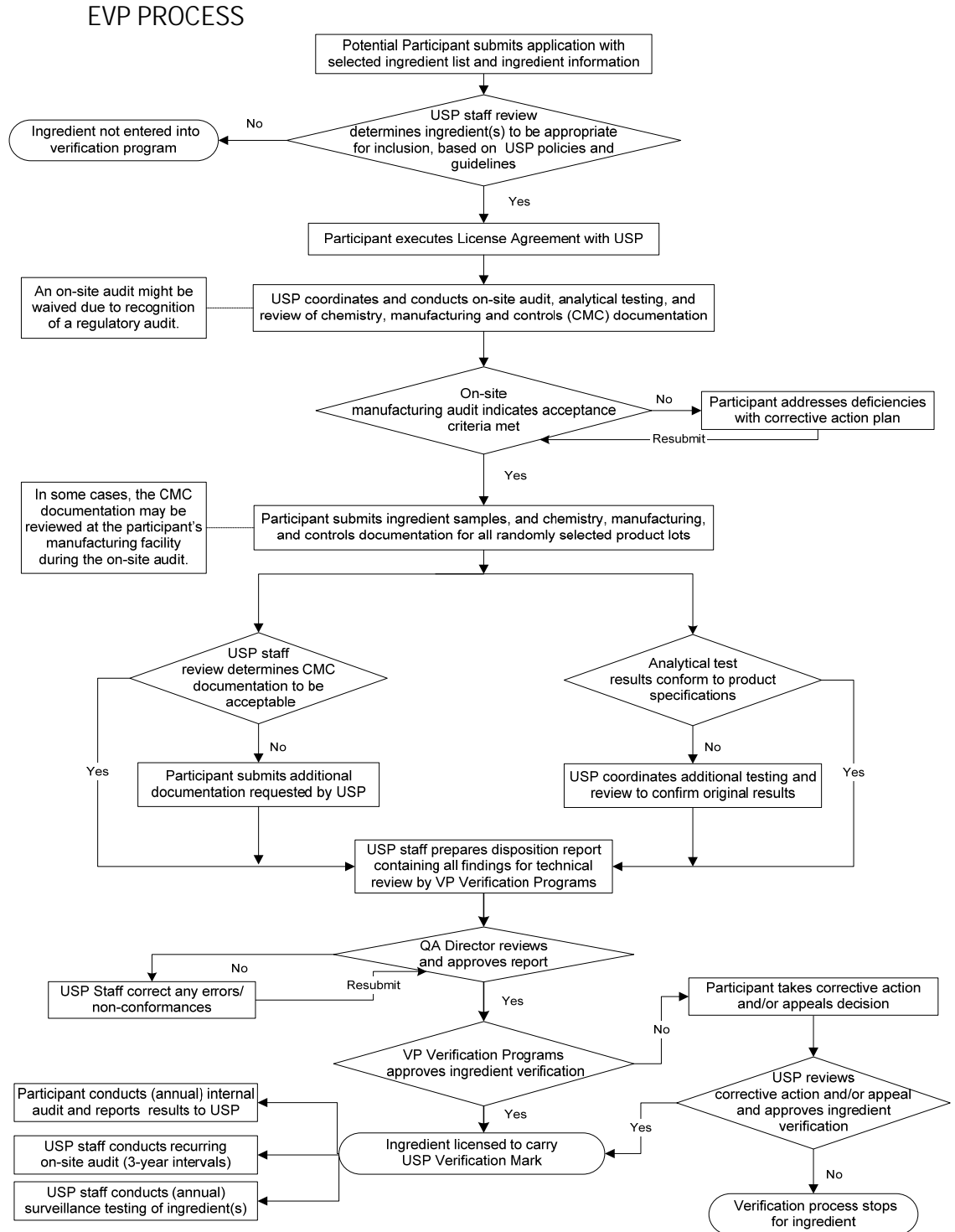
1. Initial verification audit documentation
2. Raw material specifications, test results, and raw data relating to the release of material for use
3. Excipient characterization:
 - a. Chemical and physical characterization: structure, crystallinity, state of aggregation, others, as appropriate
 - b. Impurities characterization, including impurities that are process related and that are derived from the raw material used in manufacturing
 - c. Concomitant component(s) (that is, essential minor components), including data to justify its (their) presence, if applicable
4. Toxicology data: Submission of toxicology data is not necessary if the excipient is used in an FDA-approved drug product, if it is included in the FDA Inactive Ingredient Database (IID), or if it has Generally Recognized As Safe (GRAS) status. If the excipient is used in a drug product approved for marketing in an 802 country,¹ no toxicology data are necessary. For all other excipients, toxicology data ² demonstrating that the article is safe for human use may be required to be included in the submitted documentation. These data may be reviewed by the USP Toxicology Expert Committee.
5. Excipient release: specification (physical, chemical, and microbiological), test results, and raw data supporting the results for three representative lots
6. Stability data
7. Excipient in-line, on-line, and at-line tests when used for release

¹ 802 country: Under the Federal Food, Drug, and Cosmetic Act (FD&C Act), there are provisions for exporting a drug, including certain biological drugs, for commercial distribution in another country when that drug is not approved in the U.S, depending on where else in the world the drug is approved. These countries include Australia, Canada, Israel, Japan, New Zealand, Switzerland, South Africa, and countries within the European Union or European Economic Area (the European Union and the European Free Trade Association) if the drug or device is marketed in that country or is authorized for general marketing in the European Economic Area.

² See FDA Guidance for Industry Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients at <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm079250.pdf>, and USP General Chapter <1074> Excipient Biological Safety Evaluation Guidelines.

8. Full validation data are not necessary for compendial tests where there is a *USP–NF* monograph. However, data verifying the suitability of the compendial procedure for the manufacturer’s excipient must be included in the package (see draft General Chapter <1226> *Verification of Compendial Procedures*). For noncompendial tests, appropriate validation data in compliance with General Chapter <1225> *Validation of Compendial Methods* must be included.
9. Full validation data in compliance with General Chapter <1225> *Validation of Compendial Methods* are required for all tests, when there is no *USP–NF* monograph
10. Master batch records
11. Executed batch records for selected lots of the excipient(s) under review
12. Packaging and labeling records for selected lots of the excipient(s) under review

4. PROCESS FLOW CHART



5.

EXCIPIENT ACCEPTANCE CRITERIA

Upon execution of the License Agreement, the participant submits to USP a list of excipients for which verification is sought. USP staff will review the list of excipients to confirm that the excipients are appropriate for inclusion in the Program. If so, the participant submits to USP the description of the lot number coding system and the excipient lot history (lot number, month of manufacture, manufacturing facility, and lot size) for all lots of the excipients submitted for verification that were manufactured during the past year under the current quality systems. Also, the participant submits the number of lots recalled, if any, in the past five years for the excipient(s) under consideration.

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

- Excipients that have monographs in the current *USP–NF*
- Excipients for which monographs have been proposed in *Pharmacopeial Forum (PF)* or are in press for publication in *PF*
- Excipients for which monographs are under development by the appropriate USP Expert Committee
- Excipients that have Generally Recognized As Safe (GRAS) status in U.S. law
- Excipients that are included in the FDA's Inactive Ingredient Database (IID)
- Excipients used in drug products that have been approved for marketing in an 802 country regardless of whether the excipient is used in a drug product approved for marketing in the United States
- Excipients used in drug products for which Abbreviated New Drug Applications have been approved by FDA's Office of Generic Drugs but not introduced in the market
- Excipients used in drug products for which Abbreviated New Drug Applications have received tentative approval from FDA's Office of Generic Drugs
- Excipients for which no *USP–NF* monographs exist but for which there are monographs in the *European Pharmacopoeia* and/or the *Japanese Pharmacopoeia*
- Excipients for which monographs appeared in previous revisions of the *USP–NF* but are not in the current revision and are used in drug products approved for marketing in countries other than the United States
- In certain circumstances, excipients used in drug products approved for marketing in countries with less stringent regulatory authorities, provided toxicology data demonstrating that the article is safe for human use are included in the submitted documentation (see section 3, "Required Process and Submissions")

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Excipients whose monographs have been removed from the *USP-NF* and excipients that have been 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 drug products in other countries.

6. EVALUATION OF INITIAL VERIFICATION AUDIT DOCUMENTATION

The Checklist for Initial Verification Audit Documentation (see section 19, "Forms and Checklists") is used in the Program as a tool to ascertain information about the participant, its quality systems, and critical manufacturing information, during the initial on-site audit of a manufacturing site/facility.

Prior to the on-site audit, the participant should provide USP with a copy of the company's quality manual; Standard Operating Procedure (SOP) index; site map/layout; flow chart of the manufacturing process(es) for each excipient; and organizational chart of top management, and key quality unit and production staff.

The participant should be able to provide the information listed on the Checklist for Initial Verification Audit Documentation to USP auditors, upon request during the on-site audit. The USP auditors perform a preliminary review of the information.

If the initial verification on-site audit is waived, as a result of USP recognizing an inspection by a regulatory agency in lieu of conducting its own audit (see Section 11 for details), then the participant should submit the information on the Checklist for Initial Verification Audit Documentation to USP, as requested by USP staff during the CMC documentation review process.

In evaluating the Initial Audit Documentation, the absence of any of the following listed elements will constitute deficiencies for which the participant needs to take corrective action:

Note that items tagged with an asterisk (*) should be translated into English for review by USP.

- Excipient Quality Systems
 - Quality policy*
 - Quality manual*
 - Documentation and records control procedures*
 - Change control procedures*
- Management Responsibility
 - Organizational chart of top management*
 - Quality management system planning
 - Defined management responsibility and authority
 - Management GMP representative
 - Internal communication system
- Resource Management
 - Organizational chart and qualifications of key quality unit and production personnel*

- List of consultants with qualification and service provided
- SOP Index*
- Training procedures* and records
- Personnel hygiene and sanitation procedures
- List of equipment with material of construction*
- Equipment maintenance procedures and records
- Equipment qualification program*
- Computer system management procedures
- List of utilities and maintenance procedures
- Site map and plant layout*
- Facility cleaning and maintenance procedures
- Product Realization
 - System for planning, design and development of product
 - Customer related procedures
 - Material purchasing verification and approval*
 - Flowchart of the manufacturing process(es)*
 - Master Production instructions and records*
 - Equipment cleaning procedures*
 - Identification and traceability of quality critical items*
 - Solvent recovery control procedures
 - In-process controls*
 - Validation of manufacturing processes*
 - Packaging system and labeling control procedures*
 - Storage and handling procedures
 - Delivery and distribution procedures and records
- Measurement, Analysis and Improvement
 - Customer satisfaction measurement procedures
 - Internal audit program
 - Monitoring and measurement of processes
 - Laboratory controls
 - Monitoring and measurement of product*
 - Finished excipient testing and release*
 - Control of impurities*
 - Out of specification investigation procedures*
 - Retained sample
 - Certificate of analysis*
 - Stability testing program (expiry/retest dates)*
 - Control of nonconforming product
 - Reprocessing and/or reworking procedures
 - Returned excipients handling procedures
 - Improvement*
 - Continual improvement

- Customer complaints procedures*
- Corrective action preventative action procedures*

Site Master File: If the participant has prepared a Site Master File or a Type I Drug Master File (DMF) or similar document for submission to regulatory agencies, the USP EVP may accept it in lieu of the aforementioned information. A Site Master File should also contain information about the quality assurance, the production and/or quality control of the manufacturing operations carried out at the site. The information helps in the efficient planning and implementation of the on-site audit. The Site Master File should contain general information about the site, personnel, premises and equipment, documentation, production, quality control, contract manufacture and analysis, distribution, complaints and product recall, regulatory inspections and self-inspections.

In certain cases, the participant may not have a formally established program for all aspects of the quality systems. If so, the participant can provide a description of its informal process along with a proposed plan and schedule to formalize it.

Deficiencies, if any, will be noted and provided to the participant, as part of the on-site audit report. The participant should develop corrective action plans within 30 calendar days of receipt of the notification. USP will respond to the proposed action plans within 30 calendar days of receipt. If the plan is acceptable, corrective actions must be implemented within six calendar months of receipt of USP's decision. If the information on the corrective action plan is found acceptable by USP, it will proceed with the verification process. If the participant fails to develop and implement corrective action, the verification process will be discontinued.

7 | EXCIPIENT CATEGORIZATION, SAMPLING AND SUBMISSION OF DOCUMENTATION

For cases in which a participant is submitting a limited number of excipients for verification (e.g., three), USP will select the lot(s) for each excipient to be used in the verification process. This decision will be based in part on the lot history for the excipients and the availability of the excipient lots for sampling. The lots selected will be from those manufactured at regular commercial scale. No lots manufactured under pilot scale or research and development scale will be accepted. USP may select, at a minimum, three lots for each excipient for which verification is being sought.

For the case in which a participant is submitting a large number of excipients (e.g., more than ten), attempts will be made to categorize the excipients into various groups based on scientific and quality principles. The categorization can be based on a number of factors, including the manufacturing site location and personnel, the manufacturing site quality system, the manufacturing unit operation(s) for the excipients, the chemical characteristics (e.g., chemical structure and properties), and intended use of the excipients. The participant may provide an initial categorization of the excipients for USP's review. USP may select, at a minimum, one lot of an excipient from each excipient group for evaluation.

Sample aliquots from the selected 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 excipient lot(s) and ship them via the most expedient and appropriate courier services to USP.

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

- Participant's name
- Excipient name
- Excipient item code number
- Excipient lot number
- Date sampled
- Sampler's initials
- Quantity of excipient

The participant must submit the following documentation, as specified by USP, for the chosen lot(s):

1. Chemistry, Manufacturing, and Controls (CMC) Documentation Checklist

In some cases, documentation might be reviewed at the facility. Also, the lots of excipients chosen for documentation review may not necessarily be from the same lots undergoing testing.

When a large number of excipients are being submitted for verification, the documentation request for an excipient may not necessarily involve all sections of the CMC documentation checklist. Documentation requested will focus on those elements that are of primary concern for a given excipient, based on its chemical and physical properties. For example, in the case of an inorganic salt, stability may not be the focus of the documentation review, whereas the impurity profile (absence of heavy metal contamination) may be the focus of the review. However, USP reserves the right to ask for full CMC documentation.

8 | EVALUATION OF CHEMISTRY, MANUFACTURING, AND CONTROLS DOCUMENTATION

USP will review all chemistry, manufacturing, and controls documentation submitted (See Chemistry, Manufacturing, and Controls (CMC) Documentation for Drug Substances, Dietary Ingredients, or Excipients, under Forms and Checklists, section 19) for excipients accepted into the Program. USP will determine whether the specifications (tests, analytical procedures, and acceptance criteria) provided are sufficient to demonstrate consistent and appropriate excipient quality. USP will review specifications relating to raw materials, in-process and/or intermediate materials, final excipients, packaging and labeling materials, reference materials, analytical validation data, and stability data, as well as the certificate of analysis and analytical data from the selected lots.

Note that the requested information should be submitted in the format indicated on the Chemistry, Manufacturing, and Controls (CMC) Documentation Checklist (see Forms and Checklists, section 19). The format follows that of the quality section of the Common Technical Documents (CTD). The CTD provides a harmonized structure and format for presenting CMC information for submission to the regulatory authorities in the United States, European Union, and Japan, for technical review. The requested information may be submitted electronically.

In some cases, the CMC documentation may be reviewed at the manufacturing facility during the on-site audit, however, that will increase the time and resources needed to conduct the on-site audit.

Raw Materials, Critical/Key Intermediates, and Final Excipients: For excipients for which *USP-NF*, EP, BP, and/or JP monographs exist, USP will verify conformance to the requirements specified in the monograph(s).

For excipients for which there are no compendial monographs, USP will verify that the specifications provided by the participant are adequate to ensure the identification, strength, purity, and quality, in accordance with the labeling. The specifications will be evaluated, as applicable, for

- Identification
- Content of specific entity or marker(s)
- Foreign substances and impurities
 - Heavy metals
 - Residual solvents/organic volatile impurities, USP General Chapter <467>
 - Known toxic impurities
 - Microbial contaminants
- Physicochemical properties (e.g., water, pH, melting point, optical rotation)

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

Where necessary, USP may test either all or some of the key intermediates, where these key intermediates are isolated and tested, involved in the manufacture of excipients under verification in accordance with compendial specifications (if applicable) or the specifications provided by the participant.

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

Please refer to section 10, "Specifications for Raw Material and/or Excipient," for further details on material specifications.

Applicable sections of the checklist 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 excipient (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.

Applicable sections of the checklist include 1.1 Nomenclature; and 6.0 Container Closure System.

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

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 of the checklist include 4.2 Analytical Procedures; and 4.3 Validation of Analytical Procedures

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

Applicable sections of the checklist include 5.0 Reference Standards or Materials.

Stability Data: Procedures used in stability studies will be reviewed to determine if they are able to evaluate excipient quality attributes such as appearance, content, degradation products, aggregation, and microbial counts that are susceptible to change during storage and likely to influence the excipient's quality and performance. Real-time stability studies will be used for review. If data from real-time stability studies are not available at the time of verification, then accelerated stability data may be acceptable, provided the participant follows up with submission of real-time stability data as they become available.

Applicable sections of the checklist 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 data and verify that the analytical results on the certificates of analysis, from the selected excipient lots under review, 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 General Chapter <1080> *Bulk Pharmaceutical Excipients – Certificate of Analysis*. In case of noncompliance, USP will provide recommendations for changes.

Applicable sections of the checklist include 4.4 Batch Analysis.

Manufacturing Documentation: USP will review all manufacturing documentation (submitted per Chemistry, Manufacturing and Controls (CMC) Documentation Checklist for Drug Substances, Dietary Ingredients, or Excipients, under Forms and Checklists, section 19) for excipients accepted into the Program.

The documentation submitted must include

- Master formulas/manufacturing directions/manufacturing guide
- A process diagram of chemical synthesis, extraction, secondary/tertiary recovery, fermentation, grinding, sifting, sizing, cleaning, etc., if applicable
- Acceptable procedures for reprocessing that demonstrate that the lot meets label or certificate of analysis declarations and the stability specification. Alternatively, a statement that reprocessing is not performed would suffice

- Identification of steps requiring a quality control check (particularly critical/key intermediate steps involved in synthesis, extractions, sizing, etc.)
- Executed batch records for lots that USP has selected for review

The batch records must include

- Manufacturing instructions
- Packaging instructions
- Release data related to the quality control for all key intermediates involved in the manufacture of the excipient undergoing verification
- Labeling for the subject lot
- Indication of QA final release approval

In-Process Monitoring: USP will review specifications provided by the participant for in-process control steps defined in the internal manufacturing and process directions.

Applicable sections of the checklist include 2.1 Manufactures(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 chemistry, manufacturing, and controls documentation is found 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 chemistry, manufacturing, and controls documentation is considered unacceptable and USP determines, after discussion with the participant, that the evaluation of additional information or excipient samples submitted by the participant will not add useful data, the entire chemistry, manufacturing, and controls documentation will be deemed unacceptable and the verification process will be discontinued.

If the chemistry, manufacturing, and controls documentation is considered unacceptable but, on discussion with the participant, there is sufficient cause for USP to confirm any supplied procedures and/or analytical results, the excipient 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 quality control documentation, USP will proceed to the next step in the verification process. If the laboratory results support the acceptance of the chemistry, manufacturing, and controls 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 chemistry, manufacturing, and controls documentation, the verification process will be discontinued. All such laboratory testing is performed at the participant's expense.

Drug Master File (DMF): If the participant has prepared a Type IV DMF or similar document for submission to regulatory agencies, the USP EVP may accept it in lieu of the aforementioned information. This document should address the key elements listed in this section, and should facilitate documentation submission for non-English speaking participants. As above, USP staff will inform the participant if additional information is required, for example, executed batch records may be requested.

9. TESTING OF EXCIPIENT SAMPLES

Testing of excipient samples will begin after USP has determined that the documentation regarding the excipient's specification, test procedures with appropriate validation data/report, and the certificate of analysis is complete and acceptable. Testing of excipient samples may occur in parallel with the CMC documentation review.

Excipients will be tested for critical quality attributes as determined by USP to evaluate the quality of the excipient(s) and conformance with its specification, label claims and certificate of analysis.

Please refer to section 10, "Specifications for Raw Material and/or Excipient," for further details on testing of excipient samples.

USP will coordinate testing of excipient samples in USP laboratories and/or by one or more approved contract laboratories. A single analysis will be performed for each excipient test. Test data will then be evaluated for accuracy and to determine if the excipient conforms to its 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 test results. If specific analytical errors are found, a sample retest will be requested from the laboratory. The laboratory will be asked to reanalyze the original sample, if possible, in duplicate. If the reanalyzed results agree with the initial test result, all results will be averaged and reported. If the reanalyzed results confirm the suspected analytical error, only the reanalyzed results will be averaged and reported.

In the case of nonconforming results, where there is no determinant error, the laboratory will be asked to reanalyze the original sample, if possible, in duplicate, along with a newly submitted sample of the excipient lot, in duplicate. Testing on each sample set will be performed by different experienced analysts. If the four reanalyzed results disagree with the initial test result, the average of the four reanalyzed test results will be reported. If the four reanalyzed results agree with the initial test result, all results will be averaged and reported.

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

10. SPECIFICATION FOR RAW MATERIAL AND/OR EXCIPIENT

A specification is defined as the list of tests, references to analytical test procedures, and acceptance criteria that define the standard of quality for a material to be acceptable for its intended use. The acceptance criteria may be numerical limits, ranges, or other criteria for the given test procedure. The specification establishes the set of criteria to which a raw material and/or excipient should conform to be considered acceptable for its intended use. The specification is chosen to confirm the quality of the material rather than to establish full characterization, and should focus on those characteristics that ensure the safety and suitability of the material for its intended use.

The quality of the excipient is determined, in part, by the in-process controls applied throughout manufacture and may involve key intermediates for which specifications are given. In some cases, an excipient may have more restrictive acceptance criteria for release than for the retest date of the excipient to ensure that the excipient will remain within its acceptance criteria throughout the period until its retest date. Specifications for critical intermediates, release, and shelf-life of the excipient will be reviewed by USP staff.

As previously indicated, for an excipient for which a *USP–NF*, EP, BP and/or JP monograph exists, USP will verify conformance to the requirements specified in the monograph.

For excipients for which there are no *USP–NF* monographs, USP will evaluate whether the specifications provided by the participant are adequate to ensure identification, strength, purity, and quality, in accordance with the labeling.

The following tests are considered generally applicable to excipients:

Description: A qualitative statement about the state (e.g., solid, liquid) and visual characteristics (e.g., color) of the excipient should be included.

Identification: Identification testing should be unequivocal and should be able to discriminate between materials of closely related structure that are likely to be present.

Assay: A specific, stability-indicating procedure should be included to determine the content of the excipient. If a nonspecific assay is justified, other supporting analytical procedures should be used to achieve overall specificity.

Foreign Substances and Impurities: Tests should be provided for the presence of foreign substances and impurities to ensure limited amounts of substances that are unobjectionable under the conditions in which the excipient is to be employed. Foreign substances and impurities

can arise from raw materials, from the manufacturing process, and from the degradation of the excipient. Appropriate criteria should be stated for each individual impurity and may include both identified and unidentified impurities.

(1) Organic Impurities: In some cases, it is possible to use the same procedure (e.g., HPLC) for both assay of the excipient and quantitation of the organic impurities.

(2) Inorganic Impurities: Procedures and acceptance criteria for inorganic impurities should be based on knowledge of the manufacturing process and may be determined by nonspecific tests (e.g., sulfated ash, residue on ignition) or by specific tests (e.g., atomic absorption spectroscopy).

(3) Residual Solvents: Residual solvents are organic volatile chemicals that are used or produced in the manufacture of the excipient and that are not completely removed by practical manufacturing techniques. Procedures such as those delineated in USP General Chapter <467> *Residual Solvents* should be employed, and the content of solvents in the excipient should be evaluated and justified.

Physicochemical Properties: The physical nature of the excipient may involve properties such as pH of an aqueous solution, melting point/range, and refractive index, depending on its intended use.

Particle Size: For excipients intended for use in solid or suspension drug products, particle size can have a significant effect on the drug product's dissolution rate, bioavailability, and/or stability, in which case an appropriate procedure for measuring particle size distribution and corresponding acceptance criteria should be provided.

Polymorphic Forms: Some excipients exist in crystalline forms that differ in their physical properties. Polymorphism also may include solvation or hydration products (pseudopolymorphs) and amorphous forms. In cases where differences exist that can affect the performance, bioavailability, and/or stability of the drug product, then the appropriate solid state of the excipient should be specified, and the appropriate physicochemical procedures used to determine which form(s) exist.

Water Content: This test is important in cases where the excipient is known to be hygroscopic or degraded by moisture. In some cases, a loss-on-drying procedure may be considered adequate; however, a procedure that is specific for water (e.g., Karl Fischer titration) is preferred.

Pesticides: For articles of botanical origin, pesticide testing should be conducted according to USP General Chapter <561> *Articles of Botanical Origin* or the FDA's *Pesticide Analytical Manual* (PAM) and should comply with the applicable federal regulations in the United States or with the requirements of the appropriate government body.

Undesirable Contaminants: Material of animal origin should be monitored for the potential presence of bovine spongiform encephalopathy (BSE) or transmissible spongiform

encephalopathy (TSE) material. In these cases, consult *European Pharmacopoeia (EP)* General Chapter 5.2.8, "Minimizing the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Medicinal Products" and the proposed rules of the U.S. Department of Agriculture, Animal and Plant Health Inspection Service (APHIS) published in the *Federal Register* (November 4, 2003, Volume 68, Number 213): 9 CFR Parts 93, 94, and 95, Bovine Spongiform Encephalopathy; Minimal Risk Regions and Importation of Commodities. Also, material of plant and animal origin should be monitored for the potential presence of genetically modified organism (GMO) material.

Microbial Limits: There may be a need to specify the total count of aerobic micro-organisms, the total count of yeasts and molds, and the absence of specific objectionable bacteria (e.g., *Staphylococcus aureus*, *Escherichia coli*, *Salmonella spp.*, *Pseudomonas aeruginosa*). These microbes should be suitably determined using pharmacopeial procedures (e.g., General Chapter <61> *Microbial Limit Tests*).

For questions or clarification regarding specifications for raw materials and/or excipients, please contact Program staff at 301-881-0666.

11. ON-SITE AUDIT CRITERIA

USP staff auditors and/or approved contract auditors perform the on-site audit of the participant's facilities and operations. The on-site audit will be conducted at least once every three years. In general, participants will conduct internal audits on an annual basis after successfully completing all aspects of the Program. At its sole discretion, USP may conduct additional on-site audits on a for-cause basis, in response to an Always Significant Change, or as a follow-up to the initial audit when Action Level 1 deficiencies are noted (see section 12, "USP EVP Report of Findings," and section 15, "Participant's Internal Audits, USP Audits, and Annual Reports").

USP is willing to recognize inspections carried out by regulatory agencies of countries such as the USA, Canada, Japan, Europe, United Kingdom, Australia, and other countries recognized under Section 802 of the FD&C Act. In lieu of USP conducting the audit, USP will require the full reports of such inspections conducted by the regulatory agencies for review by the USP auditors to determine whether or not to excuse the participating company from an on-site audit. Such inspections may be used in whole or in part to meet the Program requirements, depending on the documented coverage by the regulatory agency. If the inspection is acceptable in part, then an abbreviated USP on-site audit may be performed to complete the Program requirement. If the inspection is acceptable, USP would use the date of the inspection with which to determine when to conduct the next three-year on-site audit.

Criteria for waiving the GMP Audit:

1. The manufacturing site must have been inspected
 - a. By the US FDA, within the last 18 months, and no 483 had been issued. The firm must share the full agency report with USP; and/or
 - b. By other regulatory agencies such as Health Canada, Ministry of Health, Labour and Welfare (MHLW) of Japan, European Medicines Agency (EMA), Medicines and Healthcare products Regulatory Agency (MHRA) of the United Kingdom, Therapeutic Goods Administration (TGA) of Australia, within the last 18 months, and that no adverse comments were noted.
2. The firm must submit the full establishment inspection report(s) to USP for review.
3. The establishment inspection reports must include the ingredients or a group of ingredients that have been submitted to USP for verification.
4. The manufacturing site must be substantially under the same ownership and management as when the inspection(s) occurred.
5. In the event a site received a Form FDA 483 list of inspectional observations or similar adverse report, the manufacturing site must have resolved the issues to the written satisfaction of the issuing agency. The documentary evidence must be shared with the USP.
6. The site must certify in writing that no material changes in the quality systems have occurred since the regulatory inspection reports.

USP reserves the right to perform an on-site audit at the participant's expense if the CMC documentation review and/or testing results raise questions regarding the current manufacturing practices followed at the site.

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 to the participant's designated contact person the agenda for the audit, specifying all relevant areas to be covered. The participant must ensure the availability of the required personnel. Whether announced or unannounced, the principles of the *USP–NF* General Chapter <1078>, the IPEC/PQG GMP guide, and the WHO GMP guide will be followed. Safety procedures for the areas being audited will be followed.

The auditor will use the general scheme of systems approach for auditing the manufacture of excipients including the following systems:

- Materials System, which includes the measures and activities used to control the starting materials, intermediates, containers and closures; validation of computerized inventory control processes; and storage and distribution controls.
- Production System, which includes the measures and activities used to control the manufacture of excipients, in-process sampling and testing, and process validation.
- Facilities and Equipment System, which includes the activities of the firm which provide an appropriate environment and resources needed in the manufacture of excipients.
- Packaging and Labeling System, which includes the controls used in the packaging and labeling of finished excipients.
- Laboratory Control System, which includes the activities and controls used related to laboratory procedures, testing, analytical methods development and methods validation or verification, and the firm's stability program.
- Quality System, which includes the overall compliance assessment with current Good Manufacturing Practices (cGMP), and internal procedures and specifications.

The auditors will evaluate the findings of the on-site audit, using the following documents as guidance:

- *USP–NF* General Chapter <1078 > *Good Manufacturing Practices for Bulk Pharmaceutical Excipients*
- The Joint International Pharmaceutical Excipients Council and Pharmaceutical Quality Group (IPEC/PQG) *Good Manufacturing Practices Guide for Pharmaceutical Excipients*
- World Health Organization (WHO) Technical Report Series, No. 885, 1999, Annex 5: *Good manufacturing practices: supplementary guidelines for the manufacture of pharmaceutical excipient*

Auditors will apply the following criteria:

Organization/Personnel

- Dedicated quality assurance/quality control department
- Training program for the competency of all employees

Document Management

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

Equipment/Facilities

- Adequate security to prevent access of unauthorized personnel
- Adequate size and design of equipment and facilities
- Maintenance and qualification of equipment to ensure consistent performance for its intended use
- Documentation of use, calibration, cleaning, 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 materials, manufactured intermediates, and finished excipients
- System of material reconciliation

Deviations

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

Laboratory Controls

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

Label Control

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

Stability

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

Quality Assurance System

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

Validation

- Process validation for excipients submitted to the Program for verification
- Equipment cleaning validation

Electronic Records/Computerized Systems

- Proof of performance
- Appropriate security
- Appropriate backup

The on-site audit will be conducted according to the Checklist for On-site audit (see Section 19, "Forms and Checklists"). 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 deficiencies. The audit report will then be forwarded to the participant along with the Program's report of any actions that the participant needs to take to correct these deficiencies. The participant will have 30 calendar days to reply to reported deficiencies with a corrective action plan. Failure to do so may result in the discontinuation of the verification process. For Action Level 1 deficiencies (see section 12, "USP EVP Report of Findings"), proof of corrective action, with the date of completion or progress made, must be submitted to USP before the verification process can continue for the excipient. For Action Level 2 deficiencies, the verification process will continue, but deficiencies

must be addressed and corrective action taken before the verification letter can be issued for the excipient. For Action Level 3 deficiencies, proof of corrective action, with the date of completion or progress made, must be submitted to USP with the participant's first self-audit report.

12. USP EVP REPORT OF FINDINGS

The participant is notified of the final determination and status of any issues regarding the various elements of the Program that pertain to the participant. The report for each manufacturing site will be segregated according to the following elements of the Program, as applicable:

- Initial verification audit documentation
- On-site audit
- Chemistry, manufacturing, and controls documentation for all intermediates and finished excipient
- Testing for conformance to specifications

The results for initial verification audit documentation and the on-site audit apply to the manufacturing site audited and the excipients manufactured at that site, whereas the results for the remaining section(s) will be excipient specific.

The status of the issues or deficiencies within each Program element may be divided into three categories: Action Level 1, Action Level 2, and Action Level 3. These three categories differ according to the nature and potential impact of the issue or deficiency. All action level deficiencies require some action to be taken by the participant.

ACTION LEVEL 1 issues involve a lack of a quality system program element, a lack of essential excipient criteria, or excipients identified as having critical deficiencies. Action Level 1 issues may be resolved by supplying essential information or by making Always Significant Changes to an excipient or process. Action Level 1 issues require changes to the current quality system. Action Level 1 issues must be adequately resolved before the verification process can continue for the excipient, and may require that the excipient be resubmitted for verification. A follow-up on-site audit may be necessary.

ACTION LEVEL 2 issues involve a lack of information regarding a quality system program element, a lack of significant excipient criteria, or excipients identified as having major deficiencies. Action Level 2 issues may be resolved by supplying supplemental information or by making minor changes to the excipient or process. Action Level 2 issues do not require changes to the current quality system. The verification process can continue pending resolution of Action Level 2 issues, but such issues must be adequately resolved before a verification letter will be issued for the excipient.

ACTION LEVEL 3 issues involve the need for clarifying information or newly requested information regarding a quality system program element, requested improvements to excipient criteria, or excipients identified as having minor deficiencies. Action Level 3 issues may be resolved by supplying additional information or by making requested changes to the excipient or process. USP verification can be issued subject to the firm's

commitment to address the Action Level 3 issues cited within the specified time period. Failure to address an Action Level 3 issue in a timely manner could lead to revocation of verification status.

The status of each category (initial verification audit documentation; on-site audit; chemistry, manufacturing, and controls documentation; and testing for conformance to specifications) is indicated by an overall assessment of Pass or Fail, depending on the nature of the issues/deficiencies within each category. The grading system of Pass/Fail is based on the following determination:

PASS indicates that only Action Level 3 issues or deficiencies need to be resolved. Verification would be considered without further delay and will be reconsidered based on the USP follow-up audit or the participant's first self-audit report.

FAIL indicates that one or more Action Level 1 or Action Level 2 issues or deficiencies need to be resolved. The participant would need to make the appropriate change(s) to the excipient or process and most likely will need to resubmit the excipient for verification.

13. ISSUANCE AND USE OF THE USP CERTIFICATION MARK

On satisfactory completion of the items listed below for each excipient or excipient group:

- Evaluation of initial verification audit documentation
- Evaluation of on-site audit report
- Evaluation of chemistry, manufacturing, and controls documentation
- Test results of excipient samples for conformance to specifications

For each excipient or excipient group that successfully completes the Verification Program, USP will issue a Certificate of Standards Compliance. The Certificate will specify which of the participant's excipient(s) are entitled to the use of the USP Pharmaceutical Ingredient Certification Mark and other limiting information (such as manufacturing site information) as appropriate.

USP will review all labeling that will include the USP Pharmaceutical Ingredient Certification Mark for the prospective excipient. USP reserves the right to ask for additional documentation as necessary.

The mark must be used in accordance with the guidelines in the *USP Pharmaceutical Ingredient Verification Program Mark Usage Manual* and the Program License Agreement, 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 Certification Mark
- Acceptable format and materials
- Specifications for reproduction
- Examples of appropriate and inappropriate use
- Acceptable and unacceptable usage of the Certification Mark in advertising and promotional materials, exhibit signage, and educational materials; at speaking engagements, presentations, and events; and on websites

USP requires submission of artwork for excipient labels, advertising, promotions, or other materials that include the Certification 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 – if any – to be mailed must 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 calendar days. USP may, if necessary, request additional materials from the participant. Materials must conform with 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, at its discretion, also will work 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 excipients under the Program will be made available to the public on the USP website.

If the Certification Mark is misused or improperly used, USP will work with the participant licensed to use the Certification 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 Certification Mark either in its entirety or on an excipient-specific basis. The warning shall specify the steps required for the participant to come into conformance and avoid revocation or suspension, and 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 Certification Mark, either in its entirety or on an excipient-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. NEED FOR RE-EVALUATION AND RENEWAL OF VERIFICATION

After USP has granted approval to use the Certification Mark, any significant change to an excipient must be reported in writing to USP. In assessing or evaluating the significance of a change, USP General Chapter <1195> *Significant Change Guide for Bulk Pharmaceutical Excipients* should be consulted. USP General Chapter <1195> states that “a significant change is one that alters an excipient’s physical or chemical property outside the established limits, or that is likely to alter the excipient performance in the dosage form.” The participant should also notify USP in writing of any other change deemed by the participant to be essential or significant.

The following is intended only as a summary of USP General Chapter <1195>. The Participant should refer to USP General Chapter <1195> as set forth in the current edition of the *USP-NF*.

Significant Change Evaluation Criteria

<1195> *Significant Change Guide for Bulk Pharmaceutical Excipients* describes various criterion upon which to determine the significance of a change on an excipient. These include:

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

Risk Levels

In the evaluation of the effect of changes on the excipient, it is recognized that even with objective criteria that is provided in USP General Chapter <1195>, some judgment may be necessary. To facilitate the decision as to the significance of a change and the likely effect on the dosage form, the types of changes are classified using three (3) risk levels:

Level 1: Minor Change

Level 2: Might Be Significant

Level 3: Always Significant

An **Always Significant Change** (Level 3) is defined as a change that has substantial potential to have an adverse effect on the identification, strength, quality, or purity of an excipient as those characteristics may relate to the safety or intended use of the excipient. These changes are considered likely to affect the excipient’s chemical or physical properties, impurity profile, or functionality. An Always Significant Change requires notification to USP upon implementation. Such notification by the participant must be made in writing with a list of the excipients that are affected by such changes, the details of the changes, and the rationale for the changes. The

notification must include data from three lots manufactured prior to the change and three lots manufactured after the change. Upon receipt of such notification, USP will expedite the review of such change and communicate its decision as to whether or not the excipient or participant needs to be re-evaluated or the excipient retested.

A **Might Be Significant Change** (Level 2) is a change that has moderate potential to have an adverse effect on the identification, strength, quality, or purity of the excipient as those characteristics may relate to the safety or intended use of the excipient. The effect of the change should be evaluated against criteria for chemical and physical properties and impurity profile to determine its potential effect on excipient functionality. Might Be Significant Changes must be communicated by the participant to USP in the Annual Product Report (see Chapter 15) at the time the change is introduced; pre-notification is not required.

A **Minor Change** (Level 1) is a change that has minimal potential to have an adverse effect on the identification, strength, quality, or purity as those characteristics may relate to the safety and the intended use of the excipient. These changes are considered unlikely to affect the excipient's chemical or physical properties, impurity profile, or functionality. Such changes should be documented, but notifications to USP are not necessary.

Protocol Design

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

Supporting Data

There should be a written protocol for the evaluation of a change to determine whether it is significant. It is preferable to use data to measure the effect of a change on the excipient. The comparison should begin with chemical and physical properties, followed, where appropriate, by moisture, bioburden, impurity profile, and functionality. The manufacturer should use good judgment on sample comparisons for the other evaluations.

Chemical and physical properties lend themselves to quantitative measurement. Often these properties are part of the specification for the excipient. As such there should be a large body of

test data to use for the properties affected for comparison to the corresponding data of the excipient made after the change.

Equivalence of impurity profiles is shown by comparing the data for the pre-change and post-change batches. If the following conditions are met, there has been no significant change in the impurity profile. [Note – Residual Solvents <467> notes that under certain circumstances and impurity concentration below 0.10% may be of concern and the excipient manufacturer should take this under consideration.]

- (i) No new impurity is present at or above 0.10%, nor has an impurity at this level disappeared that was previously in the impurity profile.
- (ii) Residual solvent and impurities remain within the 95% confidence interval of the mean of the batches produced before the change.

Documentation

It is recommended that the evaluation of changes to the excipient be documented, regardless of the level of change. The report should indicate the basis for evaluating the effect of the change on the excipient, 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 significant.

Upon receipt of information regarding changes, USP will review and determine whether the changes are Level 1, 2, or 3. The criteria for such a determination will be made available, in writing, to the participant. If necessary, USP may require the excipient or participant to be re-evaluated or the excipient retested. If re-evaluation is not required, the participant may continue to use the USP verification status in accordance with licensed terms.

If re-evaluation is required, USP will immediately notify the participant in writing. USP also may require the participant to cease continued use of the USP verification status until the re-evaluation has been completed.

The participant may appeal the decision to require re-evaluation or retesting under the procedures described in section 17, "Appeals"; however, the participant shall not have the right to appeal the decision requiring it to cease using the USP verification status until the final decision is made regarding the status of re-evaluation or retesting.

15. PARTICIPANT'S INTERNAL AUDITS, USP AUDITS, AND ANNUAL REPORTS

Results reported from the participant's internal audits will be used to monitor the state of operations within the participant's site(s) in between audits conducted by USP.

An on-site audit will be conducted by USP at the time of initial enrollment in the Program and at the three-year renewal point. More frequent audits by USP may be conducted on a for-cause basis, in response to an Always Significant Change, or as a follow-up to the initial audit when Action Level 1 deficiencies were noted (see section 12, "USP EVP Report of Findings"). When the participant conducts an internal audit, the criteria listed in section 11, "On-Line Audit Criteria," should be consulted.

The participant must provide USP with an Annual Product Report (APR), with the first report due 13 months after the initial audit. The APR should include, but is not limited to, the following information:

- Lot numbers and dates of manufacture of all batches of verified excipients manufactured during the preceding year
- Any deviations recorded in these excipients
- Audit findings from any internal audit(s) conducted using the Checklist for On-Site Audit
- List of Always Significant and Might Be Significant Changes

If any compliance issues arise during the review of the annual product report, USP reserves the right to conduct additional on-site audits.

Participants with multinational sites will be allowed to submit their corporate audit report for the sites manufacturing the verified excipient.

16. POST-VERIFICATION SURVEILLANCE

After the Certification Mark is awarded to an excipient, USP will perform at a minimum an annual evaluation of the excipient to ensure that it continues to meet the Program criteria. Participants will be required to submit samples from their manufacturing sites to support this surveillance.

When a large number of excipients are being submitted for verification, the excipients evaluated during surveillance typically will be those excipients which did not undergo any documentation review or excipient testing during previous years.

USP will contact the participant and request a randomly selected list of the lots bearing the Certification Mark that are available for post-verification testing (requesting lot numbers and manufacturing dates). From that list, USP will randomly select a minimum of one lot for each excipient to perform post-verification testing. USP will ask the participant to send samples of the specified lot(s), or Program staff may collect samples of the lot(s) from the participant. The samples received by USP will be tested in accordance with the compendial or participant's specification. Subsequently, USP will request, at a minimum, the release specification and analytical procedures used by the participant. USP also may request further documentation based on the excipient that was verified. USP may, at its sole discretion, perform testing beyond the testing specified by the participant and will likely do so if there is a reasonable probability that the excipient contains known contaminants or degradation products.

17. APPEALS

In certain situations USP may refuse to approve the use of the Certification Mark or may suspend or revoke the use of the Certification Mark to participants. Participants may appeal the following actions by USP:

- Rejection of initial verification audit documentation; chemistry, manufacturing, and controls documentation; test results; surveillance results; or audit reports
- Recommendations for product recalls
- Suspension or revocation of the Certification Mark

An initial decision not to award the Certification Mark is final. It may not be appealed.

Rejection Based on Deficiencies in Documentation, Test Results, or Audit Reports

Among other things, USP may reject as insufficient

- Documentation that fails to meet the requirements for initial verification audit documentation, and chemistry, manufacturing, and controls documentation
- Test results that fail to demonstrate that the excipient meets the labeled amount or other acceptance criteria (for initial verification and post-verification surveillance)
- Audit reports that show deficiencies or deviations from Good Manufacturing Practices at the facility

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 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 evaluation of the participant and data at the appropriate step in the Program process. If the data and/or reports are rejected, the participant can re-enter the Program after correcting the deficiencies.

Product Recalls

USP may recommend a product recall if critical excipient deficiencies are detected. Excipient deficiencies are considered critical if

- There is even a remote probability that the use of, or exposure to, the excipient may cause serious adverse health consequences or death when used as intended.
- There is even a reasonable probability that the use of, or exposure to, the excipient may cause temporary or medically reversible adverse health consequences when used as intended.
- An official from the participant has submitted fraudulent documents to the USP.
- An official organization, such as FDA, has recommended voluntary recall.

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 excipient problem. USP will then affirm or reverse its recommendation to recall the excipient. If USP decides that a recall is to be recommended, it will immediately contact the appropriate governmental agency, such as the FDA in the United States, and notify the participant to discontinue the use of the Certification Mark on the excipient. The participant must take immediate action to do so, but it may appeal, within seven calendar days, the decision to discontinue right to use the Certification Mark. The Program License Agreement requires participants to release and hold USP harmless for any reports that it files in good faith with appropriate governmental authorities and for any decisions it makes regarding participants’ applications for continued maintenance of verification under the Program.

Suspension of the USP Verification

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

- Violation of any Program participation criteria, policies, or procedures by the participant, its affiliates, or agents.
- Major excipient deficiencies, which include a major deviation from excipient standards and/or manufacturing process.
- Always Significant Changes to an excipient’s specification, process control data, raw material source, equipment, manufacturing site change, testing, or any other change deemed essential by the participant which must immediately be reported in writing to USP. USP will review the information and determine whether or not to suspend use of the Certification Mark during re-evaluation or retesting of the excipient. 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 Certification 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 Certification 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 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 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 participant's verification status and use of the Certification Mark.
- Is substantially in compliance with the Program criteria – in which case USP will reverse the suspension and reinstate use of the 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 Certification 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 Certification Mark, a participant may re-enter the Program one year from such revocation, on payment of full fees.

18. GLOSSARY

802 Country: Under the Federal Food, Drug, and Cosmetic Act (FD&C Act), there are provisions for exporting a drug, including certain biological drugs, for commercial distribution in another country when that drug is not approved in the U.S, depending on where else in the world the drug is approved. These countries include Australia, Canada, Israel, Japan, New Zealand, Switzerland, South Africa, and countries within the European Union or European Economic Area (the European Union and the European Free Trade Association) if the drug or device is marketed in that country or is authorized for general marketing in the European Economic Area.

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

Adequate: Item/area/system/knowledge that meets basic minimum requirements.

Appeals Panel: A group of consisting of two members from appropriate USP Expert Committees, the USP Director of Quality Assurance, and additional USP staff. The Panel will have the authority to review appeals submitted by companies participating in the Program regarding (1) rejection of data, process controls, or audit reports; (2) product recalls; or (3) suspension of the use of the USP Verified Pharmaceutical Ingredient Mark.

Auditor: Any Program staff member or USP-approved audit firm/consultant that performs the on-site audit.

Batch (or Lot): A specific quantity of an excipient 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.

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

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.

Commercial Scale: The manufacturing of an excipient 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, and Japan, for technical review. This document can be located on the ICH website (www.ich.org).

Concomitant Component: A substance found in an excipient that is not the intended chemical entity, but that may be necessary for assuring the proper performance of the excipient in its intended use, and is not an impurity or a foreign substance.

Council of Experts (CoE): The standards-setting body of USP. It is composed of Expert Committee Chairs elected to five-year terms by USP's Convention members.

Critical: Used to indicate something that may cause variation in the excipient's quality attributes.

Current Quality System: The quality control system and manufacturing process in place since the last instituted change to the excipient manufacturing operation.

Drug Master File (DMF): A Drug Master File is a submission to the Food and Drug Administration (FDA) that may be used to provide confidential detailed information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of one or more human drugs. The submission of a DMF is not required by law or FDA regulation. A DMF is submitted solely at the discretion of the holder. The information contained in the DMF may be used to support an Investigational New Drug Application (IND), a New Drug Application (NDA), and Abbreviated New Drug Application (ANDA), another DMF, and Export Application, or amendments and supplements to any of these. A DMF is not approved or disapproved. Technical contents of a DMF are reviewed only in connection with the review of a IND, NDA, ANDA, or an Export Application. FDA has prepared guideline to provide DMF holders with procedures acceptable to the agency for preparing and submitting a DMF. There are five types of DMFs. Ones of interest for this manual include a Type I Manufacturing Site, Facilities, Operating Procedures, and Personnel; and a Type IV Excipient, Colorant, Flavor, Essence, or Material Used in Their Preparation. The Type IV DMF should follow the harmonized structure and format of the ICH Common Technical Document (CTD).

Expert Committee (EC): One of USP's scientific standard-setting bodies responsible for the content of *USP-NF*, the *Food Chemicals Codex*, and associated publications and organized in Collaborative Groups for topics of common interest.

European Pharmacopoeia (EP): The European Pharmacopoeia is published by the Directorate for the Quality of Medicines & HealthCare of the Council of Europe (EDQM). The monographs of the Pharmacopoeia, 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.

Excipient Deficiencies (Action Level 1): Deficiencies attributable to (1) a reasonable probability that the use of, or exposure to, the excipient may cause serious adverse health consequences or death when used as intended; (2) a remote probability that the use of, or exposure to, the excipient may cause temporary or medically reversible adverse health consequences when used as intended; (3) submission of fraudulent documents to the Program by a participant's representative; or (4) a voluntary recall recommended by an official organization, such as the FDA.

Excipient Deficiencies (Action Level 2): Deficiencies attributable to (1) deviations from excipient standards that would render the excipient unusable for its intended purpose; (2) a lack of essential excipient criteria that would render the excipient unusable for its intended purpose; or (3) the engagement of participants, affiliates, or agents in a violation of any Program participation criteria, policy, or procedure.

Excipient Deficiencies (Action Level 3): Deviations from excipient standards that show evidence of minor manufacturing and/or quality control problems.

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

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.

Foreign Substance: A component present in the excipient, but not introduced into the excipient as a consequence of its synthesis or purification and not necessary to achieve the proper performance of the excipient.

Functionality: The set of performance criteria that the excipient is intended to meet when used in a formulation.

Generally Recognized As Safe (GRAS): FDA designation that 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. GRAS designations typically occur in one of three forms:

- No comment: The FDA has reviewed a product's GRAS claim and responded with "no comment" (i.e., no further challenges on the product's GRAS status).
- Self-affirmed: The manufacturer of the chemical or substance had performed all necessary research, including the formation of an expert panel to review safety concerns, and is prepared to use these findings to defend its product's GRAS status.
- FDA pending: The manufacturer has performed all the aforementioned due diligence, and submitted to the Food & Drug Administration for GRAS approval.

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 drug to assure that such drug meets the safety requirements and has the identity and strength to meet the quality and purity characteristics that it purports or is represented to possess. GMPs are that part of quality assurance that ensures that products are consistently produced and controlled to quality standards.

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

Impurity Profile: A description of the identified and unidentified impurities present in an excipient and their acceptance criteria.

Inactive Ingredient Database (IID): IID is a database maintained by the FDA that provides information on inactive ingredients in FDA-approved drug products. This information can be used by industry as an aid in developing drug products. For new drug development purposes, once an inactive ingredient has appeared in an approved drug product for a particular route of administration, the inactive ingredient is not considered new and may require a less extensive review the next time it is included in a new drug product. For example, if a particular inactive ingredient has been approved in a certain dosage form at a certain potency, a sponsor could consider it safe for use in a similar manner for a similar type of product.

Initial Verification Audit: The first on-site audit performed at a facility manufacturing products submitted to USP for verification. The audit covers the six quality systems and critical manufacturing information.

Initial Verification Audit Documentation: Documentation provided prior to the initial verification audit that includes a copy of the company's quality manual and/or site master file, SOP index, site map/layout, and organizational chart of top management and key staff in the quality unit and production.

Intended Use: Excipients can be classified based on the function they perform in a drug product formulations. Functional categories include, but are not limited to, the following: acidifying agent, antimicrobial preservative, antioxidant, buffering agent, coating agent, color, flavors, glidant and/or anticaking, solvent, sweetening agent, tablet binder, tablet and/or capsule diluent, tablet disintegrant, tablet and/or capsule lubricant, suspending and/or viscosity-increasing agent.

Intermediate: A material produced during steps of the manufacturing process of an excipient that undergoes further chemical or physical change before it becomes the final excipient.

International Conference on Harmonization (ICH): The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use is a unique process that brings together the regulatory authorities of Europe, Japan and the United States and experts from the pharmaceutical industry in the three regions to discuss scientific and technical aspects of product registration and make 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 Ministerial (MHLW). It should provide an official standard, being required to assure the quality of medicines in Japan.

Manufacturing Documentation: The manufacturing directions, master batch formula/manufacturing guide, and executed batch records.

Mark Usage Manual: A USP document which describes the (a) terms, conditions, and placement for using the USP Mark on excipient labels and CoAs and (b) provides guidelines for advertising with the USP Mark.

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 in a 2-volume set and is available in Adobe Acrobat (pdf) format on the FDA's website.

Pilot Scale: The manufacturing of an excipient on a reduced scale by processes representative of and simulating those to be applied on a larger, production manufacturing scale.

Procedure: A detailed set of instructions (methodology) used to generate analytical data.

Quality Manual: A quality manual describes the quality management system, the quality policy and the commitment of the excipient 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 interaction between quality management processes.

Quality Assurance (QA): The sum total of the organized arrangements made with the object of ensuring all excipients are of the quality required for their intended use and that quality systems are maintained.

Quality Control (QC): The checking or testing that specifications are met.

Raw Material: Any ingredient or starting material intended for use in the manufacture of an excipient, but which is not intended to be present in the final excipient.

Recall: A participant's removal or correction of its marketed excipient directed by the USP or an official organization such as the FDA, or initiated by the participant due to a critical excipient deficiency.

Residual Solvents: Organic volatile chemicals that are used or produced in the manufacture of drug substances or excipients, or in the preparation of drug products. They are not completely removed by practical manufacturing techniques. (See USP General Chapter <467> *Residual Solvents*.)

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

Should: Used to state recommended or advisory procedures or to identify recommended equipment.

Specification: A list of tests, references to analytical test procedures, and acceptance criteria that define the standard of quality for a material to be acceptable for its intended use.

Standard Operating Procedure (SOP): Detailed written step-by-step instructions needed to perform a job or task and that helps to promote uniformity in the performance of a 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 Excipient(s): Excipient(s) chosen for evaluation to represent a group of excipients, which have been grouped based on, but not limited to, their chemical characteristics (e.g. chemical structure and properties), intended use, site of manufacturing, manufacturing unit operation, and/or the quality system under which they were manufactured.

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 this *Pharmacopeia*, as well as *General Tests and Assays*, and *General Information* Chapters.

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, in order to demonstrate identification, strength, quality, and purity of official articles.

19.

FORMS AND CHECKLISTS

- Initial Verification Audit Documentation Checklist
- Chemistry, Manufacturing, and Controls (CMC) Documentation Checklist
- On-Site Audit Checklist

Excipient Initial Audit Documentation Checklist						
Participant Information						
Name of Company/Site:						
Address:						
Year Site Established:		Number of buildings:		Size of facility:		
Total # of employees:	Manufacturing:	Quality Assurance:	Quality Control:	Other:		
Name and Title of Primary Contact:						
Phone Number:		Fax:		Email:		
Name and Title of Secondary Contact:						
Phone Number:		Fax:		Email:		
Initial Audit Documentation						
<p>Please include Standard Operating Procedures (SOPs) or descriptions of the following in the initial audit documentation package.</p>			Shaded area to be completed by USP VER Staff (If "NAC" or "MI" Box is checked, VER observation(s) will be provided to Participant. AC = Acceptable NAC = Not Acceptable MI = Missing Information N/A = Not Applicable			
			<input type="checkbox"/> AC	<input type="checkbox"/> NAC	<input type="checkbox"/> MI	<input type="checkbox"/> N/A
1. Introduction: Brief company history.			<input type="checkbox"/> AC	<input type="checkbox"/> NAC	<input type="checkbox"/> MI	<input type="checkbox"/> N/A
2. Excipient Information: List of all excipients submitted for verification, including copies of their specifications; Flow chart of their manufacturing process(es) showing material inputs/outputs and key intermediates.			<input type="checkbox"/> AC	<input type="checkbox"/> NAC	<input type="checkbox"/> MI	<input type="checkbox"/> N/A
3. General Site Information: Plant layout, including buildings identified by name, purpose, and size.			<input type="checkbox"/> AC	<input type="checkbox"/> NAC	<input type="checkbox"/> MI	<input type="checkbox"/> N/A
4. Quality Management System – Excipient Quality System: Copy of the Quality Manual describing the quality management system, the quality policy and commitment of the excipient manufacturer to apply the appropriate GMP and quality management system standards; SOPs for the identification, collection, indexing, filing, storage, maintenance, and disposition of controlled documents; SOPs for the identification, collection, indexing, filing, storage, maintenance, and disposition of records; SOPs to evaluate and approve changes that may have impact on the quality of the excipient.			<input type="checkbox"/> AC	<input type="checkbox"/> NAC	<input type="checkbox"/> MI	<input type="checkbox"/> N/A
5. Management Responsibility: Organizational chart of top management; Number of employees by department; System of compliance to regulations and standards and customer requirements; Quality policy; Quality management system planning; Responsibility and authority; Management representative; Internal communication system; Management review.			<input type="checkbox"/> AC	<input type="checkbox"/> NAC	<input type="checkbox"/> MI	<input type="checkbox"/> N/A

II. Chemistry, Manufacturing, and Controls (CMC) Documentation Checklist for Drug Substances, Dietary Ingredients, or Excipients			
PARTICIPANT INFORMATION			
COMPANY NAME			
ADDRESS			
NAME AND TITLE OF PRIMARY CONTACT			PHONE NUMBER
NAME AND TITLE OF SECONDARY CONTACT			PHONE NUMBER
INGREDIENT NAME	INGREDIENT TYPE <input type="checkbox"/> DRUG SUBSTANCE <input type="checkbox"/> DIETARY INGREDIENT <input type="checkbox"/> EXCIPIENT	INGREDIENT ITEM CODE	CMC DOCUMENTATION USP VER REFERENCE NUMBER
Ingredient Information			
Complete documentation, in the requested format, needs to be received before review begins.			
<p><i>Note: In some instances (e.g. more than one drug substance, manufacturing site, manufacturing process, etc.) information may be repeated or presented separately in multiple sections, in which case, it should be made clear what the section refers to by creating distinguishing title in parentheses (Name, manufacturer) following the section header. Cross references to information in other sections is acceptable. ICH guidelines that apply to a given section are referenced at the end of the section, in parentheses.</i></p>			SHADED AREA TO BE COMPLETED BY USP VER Staff (If "NAC" or "MI" Box is checked, USP VER observation will be provided on the VER observation form and coded under Section ID as "II 1.1, II 1.2, etc." to assign appropriate observation to Form and Section.)
Contents of the Ingredient Information to be provided			AC = Acceptable NAC = Not Acceptable MI = Missing Information N/A = Not Applicable
1.0 General Information:			
1.1 Nomenclature: <i>International Nonproprietary Name, Compendial name, Chemical name, Company or laboratory code, Chemical Abstracts Service registry number, other non-proprietary name(s)</i>			<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> AC NAC MI N/A
1.2 Structure: <i>The structural formula, including relative and absolute stereochemistry, the molecular formula, and the relative molecular mass</i>			<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> AC NAC MI N/A
1.3 General Properties: <i>A list of physicochemical and other relevant properties of the drug substance. (ICH Q6A)</i>			<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> AC NAC MI N/A
2.0 Manufacture:			
2.1 Manufacturer(s): <i>The name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing</i>			<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> AC NAC MI N/A
2.2 Description of Manufacturing Process and Process Controls: <i>A flow diagram of the synthetic process(es) should be provided that includes molecular formulae, weights, yield ranges, chemical structures of starting materials, intermediates, reagents and ingredient reflecting stereochemistry,</i>			<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> AC NAC MI N/A

II. Chemistry, Manufacturing, and Controls (CMC) Documentation Checklist for Drug Substances, Dietary Ingredients, or Excipients				
<i>and identifies operating conditions and solvents.</i>				
<i>A sequential procedural narrative of the manufacturing process should be submitted. The narrative should include, for example, quantities of raw materials, solvents, catalysts and reagents reflecting the representative batch scale for commercial manufacture, identification of critical steps, process controls, equipment and operating conditions (e.g., temperature, pressure, pH, time).</i>				
2.2.1 Alternate Processes: <i>Alternate processes should be explained and described with the same level of detail as the primary process. Reprocessing steps should be identified and justified. Any data to support this justification should be either referenced or provided as part of the file (in Section 2.5).</i>	<input type="checkbox"/> AC	<input type="checkbox"/> NAC	<input type="checkbox"/> MI	<input type="checkbox"/> N/A
2.3 Control of Materials: <i>Materials used in the manufacture of the ingredient (e.g., raw materials, starting materials, solvents, reagents, catalysts) should be listed identifying where each material is used in the process. Information on the quality and control of these materials should be provided. Information demonstrating that materials (including biologically-sourced materials, e.g., media components, monoclonal antibodies, enzymes) meet standards appropriate for their intended use (including the clearance or control of adventitious agents) should be provided, as appropriate. For biologically-sourced materials, this can include information regarding the source, manufacture, and characterization (ICH Q6A and Q6B).</i>	<input type="checkbox"/> AC	<input type="checkbox"/> NAC	<input type="checkbox"/> MI	<input type="checkbox"/> N/A
2.4 Controls of Critical Steps and Intermediates: <i>Critical Steps: Tests and acceptance criteria (with justification including experimental data) performed at critical steps identified in the manufacturing process to ensure that the process is controlled should be provided. For Intermediates, information on the quality and control of intermediates isolated during the process should be provided (ICH Q6A and Q6B).</i>	<input type="checkbox"/> AC	<input type="checkbox"/> NAC	<input type="checkbox"/> MI	<input type="checkbox"/> N/A
2.5 Process Validation and/or Evaluation: <i>Process validation report should be included. Evaluation studies for aseptic processing and sterilization should be included, when applicable..</i>	<input type="checkbox"/> AC	<input type="checkbox"/> NAC	<input type="checkbox"/> MI	<input type="checkbox"/> N/A
2.6 Manufacturing Process Development: <i>The developmental history of the manufacturing process, as described in Section 2.2, should be provided. A description and discussion should be provided of the significant changes made to the manufacturing process and/or manufacturing site or critical equipment of the ingredient used in producing nonclinical, clinical, scale-up, pilot, and/or production scale batches. The reason for the changes should be explained. The significance of each change should be assessed by evaluating its potential to impact the quality of the ingredient and/or intermediate, if appropriate (ICH Q3A).</i>	<input type="checkbox"/> AC	<input type="checkbox"/> NAC	<input type="checkbox"/> MI	<input type="checkbox"/> N/A
3.0 Characterization:				
3.1 Elucidation of Structure and other Characteristics: <i>Confirmation of structure based on e.g., synthetic route and spectral analyses should be provided. Information such as the potential for isomerism, the identification of stereochemistry, or the potential for forming polymorphs should also be included (ICH Q6A).</i>	<input type="checkbox"/> AC	<input type="checkbox"/> NAC	<input type="checkbox"/> MI	<input type="checkbox"/> N/A
3.2 Impurities: <i>Information on impurities should be provided (ICH Q3A, Q3C, and Q6A).</i>	<input type="checkbox"/> AC	<input type="checkbox"/> NAC	<input type="checkbox"/> MI	<input type="checkbox"/> N/A
4.0 Control of Ingredient:				
4.1 Specifications: <i>The specifications for the ingredient should be provided (ICH Q6A).</i>	<input type="checkbox"/> AC	<input type="checkbox"/> NAC	<input type="checkbox"/> MI	<input type="checkbox"/> N/A
4.2 Analytical Procedures: <i>The analytical procedures used for testing the ingredient should be provided (ICH Q6A).</i>	<input type="checkbox"/> AC	<input type="checkbox"/> NAC	<input type="checkbox"/> MI	<input type="checkbox"/> N/A
4.3 Validation of Analytical Procedures: <i>The analytical validation information, including experimental data for the analytical procedures used for testing the ingredient should be provided (ICH Q2A and Q2B).</i>	<input type="checkbox"/> AC	<input type="checkbox"/> NAC	<input type="checkbox"/> MI	<input type="checkbox"/> N/A
4.4 Batch Analyses: <i>A copy of master batch records and executed batch records for batches selected</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

II. Chemistry, Manufacturing, and Controls (CMC) Documentation Checklist for Drug Substances, Dietary Ingredients, or Excipients				
<i>by USP should be provided. Description of selected batches and results of batch analyses should be provided (ICH Q3A, Q3C and Q6A).</i>	AC	NAC	MI	N/A
4.5 Justification of Specification: <i>Justification for the ingredient specification should be provided (ICH Q3A, Q3C and Q6A).</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	AC	NAC	MI	N/A
5.0 Reference Standards or Materials: <i>Information on the reference standards or reference materials used for testing of the ingredient should be provided (ICH Q6A).</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	AC	NAC	MI	N/A
6.0 Container Closure System: <i>A description of the container closure system(s) should be provided, including the identity of materials of construction of each primary packaging component, and their specifications. The specifications should include description and identification (and critical dimensions with drawings, where appropriate). Non-compendial methods (with validation) should be included, where appropriate.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	AC	NAC	MI	N/A
<i>For non-functional secondary packaging components (e.g., those that do not provide additional protection), only a brief description should be provided. For functional secondary packaging components, additional information should be provided.</i>				
<i>The suitability should be discussed with respect to, for example, choice of materials, protection from moisture and light, compatibility of the materials of construction with the pharmaceutical ingredient, including sorption to container and leaching, and/or safety of materials of construction.</i>				
7.0 Stability:				
7.1 Stability Summary and Conclusions: <i>The types of studies conducted, protocols used, and the results of the studies should be summarized. The summary should include results, for example, from forced degradation studies and stress conditions, as well as conclusions with respect to storage conditions and retest date or shelf-life, as appropriate (ICH Q1A and Q1B).</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	AC	NAC	MI	N/A
7.2 Post-approval Stability Protocol and Stability Commitment: <i>The post-approval stability protocol and stability commitment should be provided (ICH Q1A).</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	AC	NAC	MI	N/A
7.3 Stability Data: <i>Results of the stability studies (e.g., forced degradation studies and stress conditions) should be presented in an appropriate format such as tabular, graphical, or narrative. Information on the analytical procedures used to generate the data and validation of these procedures should be included (ICH Q1A, Q1B, Q2A, and Q2B).</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	AC	NAC	MI	N/A
8.0 Facilities and Equipment: <i>A diagram should be provided illustrating the manufacturing flow including movement of raw materials, personnel, waste, and intermediate(s) in and out of the manufacturing areas. Information should be presented with respect to adjacent areas or rooms that may be of concern for maintaining integrity of the product.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	AC	NAC	MI	N/A
<i>Information on all developmental or commercial products manufactured or manipulated in the same areas as the applicant's product should be included.</i>				
<i>A summary description of product-contact equipment, and its use (dedicated or multi-use) should be provided. Information on preparation, cleaning, sterilization, and storage of specified equipment and materials should be included, as appropriate.</i>				
<i>Information should be included on procedures (e.g., cleaning and production scheduling) and design features of the facility (e.g., area classifications) to prevent contamination or cross-contamination of areas and equipment.</i>				
9.0 Adventitious Agents Safety Evaluation: <i>Information assessing the risk with respect to potential contamination with adventitious agents should be provided in this section. Detailed information</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	AC	NAC	MI	N/A

USP Excipient Verification Program Good Manufacturing Practices On-Site Audit Checklist

Company Name:
Date(s) of Audit:
Address of Manufacturing Site:
Name and Title of Escorts:
Name and Title of Auditors:

Note: This checklist is designed as an aid or tool to be used by experienced auditors in conducting audits. It is not necessarily intended to be all-inclusive or to limit the scope of the audit. Ideally, one lot of excipient should be tracked from the start of production to release of the final material. This checklist, follows the sections in the guidance document prepared by the International Pharmaceutical Excipients Council (IPEC) and the Pharmaceutical Quality Group (PQG) entitled “The Joint IPEC – PQG Good Manufacturing Practices Guide for Pharmaceutical Excipients 2006” and in accordance with the USP-NF General Chapter <1078> *Good Manufacturing Practices for Bulk Pharmaceutical Excipients*.

INDEX FOR CHECKLIST:

1. INTRODUCTION
2. EXCIPIENT INFORMATION
3. GENERAL SITE INFORMATION
4. QUALITY MANAGEMENT SYSTEM – EXCIPIENT QUALITY SYSTEM
5. MANAGEMENT RESPONSIBILITY
6. RESOURCE MANAGEMENT
7. PRODUCT REALIZATION
8. MEASUREMENT, ANALYSIS AND IMPROVEMENT

EXCIPIENT GMP ON-SITE AUDIT CHECKLIST	ACCEPTABLE (A)	NOT ACCEPTABLE (NAc)	NOT APPLICABLE (NAp)	NOT REVIEWED (NR)	COMMENTS OR (C/A) ATTACHMENTS (√= YES)
GMP ITEM					
1.0 INTRODUCTION					
1.1 Brief company history.					
2.0 EXCIPIENT INFORMATION					
2.1 List of excipients undergoing evaluation, including their item code and a copy of their specifications					
2.2 Excipients are manufactured by (√ all that apply): <input type="checkbox"/> Chemical synthesis <input type="checkbox"/> Extraction <input type="checkbox"/> Cell culture/fermentation <input type="checkbox"/> Recovery from natural sources					
2.3 Is the manufacturing process for the excipient(s) a batch or continuous process?					
2.4 Flow chart of the manufacturing process for the excipients undergoing evaluation.					
2.5 Company should designate and document the rationale for the point at which production of the excipient according to GMPs begins.					
2.6 Excipients are used for what application?					
2.7 Are excipients used for any special applications (√ all that apply)?: <input type="checkbox"/> Parenteral <input type="checkbox"/> Ocular <input type="checkbox"/> Inhalation <input type="checkbox"/> Open wound use <input type="checkbox"/> Other <input type="checkbox"/> None					
2.8 Are excipients purported to be (√ all that apply): <input type="checkbox"/> Sterile <input type="checkbox"/> Pyrogen free <input type="checkbox"/> Other <input type="checkbox"/> None					
2.9 Other sites/companies involved in operations of the excipients undergoing evaluation and their location and manufacturing purpose.					
3.0 GENERAL SITE INFORMATION					
3.1 Number of buildings at the site.					
3.2 Size of site in terms of total area and building square footage.					
3.3 Other excipient(s), ingredient(s), or product(s) manufactured at the site.					
3.4 Are buildings solely dedicated to the manufacture of the excipients under evaluation?					
3.5 Status of last FDA or other regulatory inspection and copy of report(s), if possible.					

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GMP ITEM	A	NAc	NAP	NR	C/A
4.0 QUALITY MANAGEMENT – EXCIPIENT QUALITY SYSTEM					
4.1 General Requirements					
4.1.1 Does the excipient manufacturer identify the quality management processes required to assure excipient quality?					
4.1.1.1 Is there a quality unit that is independent of production and that fulfills both quality assurance (QA) and quality control (QC) responsibilities?					
4.1.1.2 Does the excipient manufacture instill the principle that quality is the responsibility of all persons involved in manufacturing?					
4.1.2 Does the excipient manufacturer maintain responsibility for, and define quality control measures for outsourced manufacturing, testing or other operations that could affect excipient quality (see also 7.4.2)?					
4.2 Documentation Requirements					
4.2.1 General					
4.2.1 Has the excipient manufacture established, documented, and implemented an effective system for managing quality that encompasses the organizational structure, procedures, processes and resources, and manufacturing activities?					
4.2.2 Quality Manual					
4.2.2.1 Does the excipient manufacturer have a quality manual, and if so what is the current version of it, and if not, is there a suitable alternative?					
4.2.2.2 Does the quality manual contain a description of the quality management system?					
4.2.2.3 Does the quality manual contain the company quality policy statement?					
4.2.2.4 Does the quality manual contain a commitment to apply the appropriate GMP and quality management standards contained in the quality manual?					
4.2.2.5 Has the manufacturer defined the point at which GMP should be applied and maintained?					
4.2.2.6 Does the quality manual contain the scope of the quality management system, reference to supporting procedures and a description of the interaction between quality management processes (e.g. control of records, change control system, etc.)?					
4.2.3 Control of Documents					
4.2.3.1 Has the excipient manufacturer established and maintained Standard Operating Procedures (SOPs) for the identification, collection, indexing, filing, storage, maintenance, and disposition of controlled document, including documents of external origin that are a part of the quality management system?					
4.2.3.1.1 Is there a list of SOPs for areas of the operation affecting quality?					
4.2.3.1.2 Is there a procedure for writing, handling and updating SOPs?					
4.2.3.2 Are procedures used in the manufacture of excipients documented, implemented and maintained for activities such as the identity and quantity of raw materials, equipment use and operating parameters, manufacturing process flow, in-process sampling, equipment cleaning, packaging materials, labeling, and documentation of each significant step?					
4.2.3.3 Are there established formal controls relating to procedure approvals, revisions, and distribution, that provide assurance that the current version of a procedure is being used throughout the operational areas and previous revisions of documents have been removed?					

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GMP ITEM	A	NAC	NAP	NR	C/A
4.2.3.3.1 Do documents include a unique identifier, (e.g. date of issuance and/or revision number) to facilitate identification of the current document?					
4.2.3.3.2 Are SOPs for manufacturing instructions and test methods made readily available to employees?					
4.2.3.3.3 Are current versions of procedures being used throughout the operational areas?					
4.2.3.4 Are changes to documents reviewed and approved by designated qualified personnel, or by the quality unit if the document affects product quality, before issuance to the appropriate area, as identified in the documents (see also 5.5.1)?					
4.2.3.4.1 Do documents identify the department and authorized persons with the responsibility for issuing, reviewing and/or approving the document?					
4.2.3.4.2 Are the history of changes and the reasons for the changes documented, and if so, how?					
4.2.3.5 Are electronic records used?					
4.2.3.5.1 Do electronic documentation meet the requirements of the document control system?					
4.2.3.5.2 If electronic signatures are used on documents, are they controlled to provide equivalent security to that given by a hand written signature?					
4.2.3.5.3 Do electronic documents and signatures satisfy local regulatory requirements?					
4.2.4 Control of Records					
4.2.4.1 Are SOPs established and maintained for the identification, collection, indexing, filing, storage, maintenance, and disposition of records?					
4.2.4.2 Are records maintained in such a manner to demonstrate achievement of the required quality and effective operation of the quality management system?					
4.2.4.3 Are records legible and identifiable with the product involved?					
4.2.4.4 Do pertinent subcontractor quality data meet the same requirements as that for the excipient manufacture?					
4.2.4.5 Are records clear, indelible, made directly after performing the activity (in the order performed), signed and dated by the person making the entry?					
4.2.4.6 Are corrections to entries, signed and dated, leaving the original entry legible?					
4.2.4.7 Are records kept for a specified period, based on the appropriate expiry date or re-evaluation date for each excipient?					
4.2.4.8 Are records stored and maintained in such a manner that they are easily retrievable in facilities with suitable environment to minimize damage?					
4.3 Change Control					
4.3.1 Has the excipient manufacturer established and maintained SOPs to evaluate and approve changes that may have impact on the quality of the excipient?					
4.3.1.1 Does it include changes to raw materials or packaging and their sources, material specifications, test methods, manufacturing and analytical equipment, production processes, or manufacturing or packaging sites?					
4.3.2 Does an independent department, such as Quality Assurance or Regulatory Affairs, have the responsibility and authority for the final approval of changes?					

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GMP ITEM	A	N/Ac	N/Ap	NR	C/A
4.3.3 Are customers and regulatory authorities (e.g. DMFs) notified of significant changes from established production and process control procedures that may affect the quality of the excipient?					
4.3.3.1 Is there a SOP that describes the criteria (e.g. IPEC-Americas Significant Change Guide for Bulk Pharmaceutical Excipients) used to determine when to notify customers and/or regulatory authorities of significant changes based on the likelihood that a proposed change will impact a drug product?					
4.3 Change Control					
4.3.1 Has the excipient manufacturer established and maintained SOPs to evaluate and approve changes that may have impact on the quality of the excipient?					
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5. MANAGEMENT RESPONSIBILITY					
5.1 Management Commitment					
5.1.1 Does top management demonstrate to the organization the importance of customer satisfaction and compliance with appropriate regulations and standards?					
5.1.2 Is this accomplished through development of a quality policy and establishment of quality objectives?					
5.1.3 Are the quality policy and quality objectives communicated to all employees?					
5.1.4 Is progress towards the documented the quality objectives reviewed at planned intervals?					
5.2 Customer Focus					
5.2.1 Is top management involved to ensure that customer requirements are determined and met?					
5.2.2 Are customers or their representatives allowed to conduct audits to review its quality management system, manufacturing processes, buildings and facilities?					
5.3 Quality Policy					
5.3.1 Does top management demonstrate commitment to the corporate quality policy and ensure its implemented within the operational unit?					
5.3.2 Does the quality policy support continual improvement of the quality management system?					
5.3.3 Does management participate in the development of the corporate quality policy?					
5.3.4 Does management provide the resources necessary for the development, maintenance, and deployment of the company's quality policy?					
5.4 Planning					
5.4.1 Quality Objectives					
5.4.1.1 Has top management set objectives for adherence to GMP to ensure that the excipient manufacturer maintains and improves its performance?					
5.4.1.2 Are quality objectives deployed throughout the organization?					
5.4.1.3 Are quality objectives measurable and consistent with the quality policy?					
5.4.2 Quality Management System Planning					
5.4.2.1 Has top management provided adequate resources to ensure conformance to the provisions of this guide?					
5.4.2.2 Does the Excipient Manufacture have a system in place to identify the resources needed for adherence to GMP?					
5.4.2.3 Has a gap analysis, based on audits by internal personnel, customers, regulatory agency, or outside contractor, and this guide, been conducted to identify resource requirements?					
5.4.2.4 Does top management ensure that the integrity of the quality management system is maintained when changes are planned and implemented?					

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GMP ITEM	A	NAc	NAP	NR	C/A
5.5 Responsibility, Authority, and Communication					
5.5.1 Responsibility and Authority					
5.5.1.1 Has top management clearly defined the responsibility and authority and communicated it within the company?					
5.5.1.2 Is there a unit independent of production, such as the quality unit, responsible for:					
5.5.1.2.1 Ensuring that quality-critical activities are undertaken?					
5.5.1.2.2 Approving suppliers of quality-critical materials and services?					
5.5.1.2.3 Approving or rejecting raw materials, packaging components, intermediates, and finished excipients?					
5.5.1.2.4 Ensuring review of production records, and ensuring that no errors have occurred or, if errors or discrepancies occur, that they are fully investigated?					
5.5.1.2.5 Participating in reviewing and authorizing changes to processes, specifications, procedures, and test methods that potentially affect excipient quality (see 4.3 also)?					
5.5.1.2.6 Investigating failures and complaints?					
5.5.1.2.7 Retaining responsibility for approving or rejecting the excipient if it is produced, processed, packaged or held under contract by another company?					
5.5.1.2.8 Developing and implementing a self-inspection program for the quality management system?					
5.5.1.3 Are some of the quality unit's functions delegated to other department personnel, and if so, are appropriate controls in place (e.g. periodic audits, training, and documentation)?					
5.5.1.4 Is there an organizational chart by function showing inter-departmental relationships as well as relationships to top management of the company?					
5.5.1.5 Are there written job descriptions for key personnel who have an impact on excipient quality?					
5.5.2 Management Representative					
5.5.2.1 Is there an appointed management representative with sufficient authority to ensure that this guide's provisions are properly implemented?					
5.5.2.2 Does the representative periodically report to top management on conformance to the quality management system, including changing customer and regulatory requirements?					
5.5.3 Internal Communication					
5.5.3.1 Are there appropriate systems established to communicate GMP and regulatory requirements, quality policies, quality objectives and procedures throughout the organization?					
5.5.3.2 Do the communications provide information about the effectiveness of the quality management system?					
5.5.3.3 Is there a documented procedure to ensure that top management is notified, in a timely manner, of quality-critical situations, such as product retrievals?					
5.6 Management Review					
5.6.1 General					
5.6.1.1 Does top management of the company hold periodic reviews of the quality management system to confirm the organization's continued conformance to this guide?					
5.6.1.2 Are the periodic reviews recorded and include assessing opportunities for improvement and the need for changes to the quality management system?					
5.6.2 Review Input					
5.6.2.1 Do management review inputs include: results of internal and external audits; customer feedback of the company performance; product conformity and process performance; action items from the previous management review; customer complaints; status of corrective or preventive actions; and changes that could affect the quality management system?					
5.6.3 Review Output					
5.6.3.1 Do management reviews identify the resources needed and opportunities presented for improvement of the quality management system, and improvement of product conformance to customer and regulatory requirement?					
5.6.3.2 Is a record made of actions recommended and taken?					

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GMP ITEM	A	NAC	NAP	NR	C/A
6.0 RESOURCE MANAGEMENT					
6.1 Provision of Resources					
6.1.1 Are there sufficient qualified personnel and resources (e.g. equipment, materials, buildings and facilities) to implement, maintain and improve the quality management system and to produce, package, test, store, and release each excipient in a manner consistent with this guide?					
6.2 Human Resources					
6.2.1 General					
6.2.1.1 Do personnel performing work affecting the quality of excipients have the appropriate combination of education, training, and experience for their assigned tasks?					
6.2.1.2 Do consultants advising on the design, production, packaging, testing or storage of excipients have the education, training and experience, or any combination thereof, to advise on the subject for which they are retained?					
6.2.1.3 Are records maintained listing the name, address and qualifications of consultants and the type of service they provide?					
6.2.2 Competence, Awareness and Training					
6.2.2.1 Are there written procedures for identifying training needs and providing the necessary training to personnel performing activities affecting excipient quality?					
6.2.2.2 Are employee training records maintained?					
6.2.2.3 Does the training program address the particular operations that an employee performs and GMP as it relates to the employee's functions?					
6.2.2.4 Do only qualified individuals conduct GMP training with sufficient frequency to ensure that employees remain familiar with applicable GMP principles?					
6.2.2.5 Is there adequate and continued personal hygiene training for personnel who handle materials so that they understand the precautions necessary to prevent contamination of excipients?					
6.2.2.6 Does the training program ensure that personnel understand that deviations from procedures may have an impact on the customer's product quality?					
6.2.3 Personnel Hygiene					
6.2.3.1 To protect excipients from contamination, are apparel such as head, face, hand and arm coverings worn as appropriate to the duties performed?					
6.2.3.2 Are jewelry and other loose items, including those in pockets removed or covered?					
6.2.3.3 Are only authorized personnel allowed to enter those areas of the buildings and facilities designated as limited access areas?					
6.2.3.4 Do employees practice good sanitation and health habits?					
6.2.3.5 Is anyone shown to have an apparent illness or open lesion (either by medical examination or supervisory observation) that may adversely affect the safety or quality of the excipient excluded from direct contact with raw materials, packaging components, intermediates, and finished excipients until the condition is corrected or determined by competent personnel not to jeopardize the safety or quality of the excipient?					
6.2.3.6 Are personnel instructed to report to supervisory personnel any health conditions that may have an adverse effect on excipients?					
6.2.3.7 Are the storage and use of food, drink, personal medications, tobacco products, or similar items restricted to certain designated locations separate from manufacturing areas?					
6.3 Infrastructure					
6.3.0 Is the infrastructure managed, operated, cleaned, and maintained in accordance with GMP principles to ensure excipient quality and to avoid contamination (including where critical to excipient quality, control of particulate matter, microbiological control, and control of water quality)?					
6.3.1 Building and Facilities					
6.3.1.1 Does the Excipient Manufacturer have a written procedure regarding the building and facilities operation?					
6.3.1.2 Was the prevention of contamination taken into consideration in the design of the manufacturing processes and facilities, particularly where the excipient is exposed?					
6.3.1.3 Are buildings and facilities used in the production, processing, packaging, testing or storage of an excipient maintained in a good state of repair and of suitable size, construction, and location to facilitate cleaning, maintenance and correct operation appropriate to the type of processing?					
6.3.1.4 Are manufacturing processes associated with the production of highly sensitizing or toxic products (e.g. herbicides, pesticides, etc.) located in dedicated facilities or use equipment separate from that used for excipient manufacture?					

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GMP ITEM	A	NAC	NAP	NR	C/A
6.3.1.5 Are appropriate measures (e.g. cleaning, inactivation, etc.) implemented to avoid cross-contamination, and is the effectiveness of these measures demonstrated and documented?					
6.3.1.6 Are there adequate facilities for the testing of raw materials, packaging components, intermediates, and finished excipients?					
6.3.2 Equipment					
6.3.2.1 Is the equipment used in the production, processing, packaging, testing or storage of an excipient maintained in a good state of repair, and of suitable size, construction and location to facilitate cleaning, maintenance and correct operation, depending on the type of processing (e.g. batch versus continuous)?					
6.3.2.2 Has the equipment been commissioned before use to ensure that it is functioning as intended?					
6.3.2.2.1 Ideally, has an Installation Qualification (IQ), Operational Qualification (OQ), and Performance Qualification (PQ) been performed on the equipment?					
6.3.2.3 Where equipment is located outdoors are there suitable controls to minimize the risk to excipient quality from the environment (e.g. processing within a closed system)?					
6.3.2.1 Equipment Construction					
6.3.2.1.1 Is process equipment constructed so that contact surfaces will not be reactive, additive, or absorptive and thus not alter the quality of the excipient?					
6.3.2.1.2 Are substances required for operation, such as lubricants or coolants, controlled so that they do not come in contact with raw materials, packaging materials, intermediates, or finished excipients?					
6.3.2.1.2.1 Where contact is possible, are substances suitable for use in food applications utilized?					
6.3.2.1.3 Is equipment designed to minimize the possibility of contamination caused by direct operator contact in such activities as the unloading of centrifuge bags, use of transfer hoses (particularly those used to transfer powders) and the operation of drying equipment and pumps?					
6.3.2.1.4 Is the sanitary design of transfer and processing equipment evaluated?					
6.3.2.1.5 Is equipment with moving parts assessed with regard to the integrity of seals and packing materials to control the risk of contamination?					
6.3.2.2 Equipment Maintenance					
6.3.2.2.1 Are documented procedures established for the maintenance of critical equipment used in the production, processing, packaging, testing, or holding of the excipient?					
6.3.2.2.2 Are records maintained of the use and maintenance of quality-critical equipment?					
6.3.2.2.3 Are records maintained in the form of a log, computer database, or other appropriate documentation?					
6.3.2.3 Computer Systems					
6.3.2.3.1 For computer systems that may impact excipient quality, are there sufficient controls for their operation and maintenance, and for the prevention of unauthorized access or changes to computer software, hardware, or data, including:					
6.3.2.3.1.1 Systems and procedures that show the equipment and software are performing as intended?					
6.3.2.3.1.2 Procedures for checking the equipment at appropriate intervals?					
6.3.2.3.1.3 Retention of suitable back-up or archival systems such as copies of the program and files?					
6.3.2.3.1.4 Assurance that changes are verified and documented and only made by authorized personnel?					

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GMP ITEM	A	NAc	NAP	NR	C/A
6.3.3 Utilities					
6.3.3.1 Are utilities (e.g. nitrogen, compressed air, steam, etc.) used in the production, storage or transfer of materials that could affect excipient quality assessed and appropriate action taken to control the risk of contamination and cross-contamination?					
6.3.4 Water					
6.3.4.1 Is water used in the manufacturer of excipients demonstrated to be of suitable quality for its intended use?					
6.3.4.1.1 At minimum, unless otherwise justified, does process water meet World Health Organization (WHO) guidelines for drinking (potable) water quality?					
6.3.4.2 If drinking (potable) water is insufficient to assure quality or tighter chemical and/or microbiological water quality specifications are required, are appropriate controls and specifications set (e.g. physical and chemical attributes, total microbial counts, limits on objectionable organisms and/or endotoxins)?					
6.3.4.3 Where water used in the process is treated by the manufacturer to achieve a defined quality, is the treatment process specified and monitored with appropriate action limits?					
6.3.4.4 Is water that comes into contact with the excipient supplied under continuous positive pressure (or other means of preventing back flow) in a system free of defects to control the risk of contamination to the excipient?					
6.4 Work Environment					
6.4.0 Where the excipient is exposed during manufacture, is it in an appropriate environment to minimize contamination, and does the manufacturer apply suitable controls to maintain the environment?					
6.4.1 Air Handling					
6.4.1.1 Where an air handling system is installed to provide protection to the excipient, has the excipient manufacturer demonstrated and documented its effectiveness?					
6.4.1.2 Is excipient production unit air handling systems designed to prevent cross contamination?					
6.4.1.2.1 For dedicated areas processing the same excipient, it is permissible to recycle a portion of the exhaust air back into the same area. Is this case here?					
6.4.1.3 For multi-use areas, especially if several products are processed simultaneously, is the adequacy of the air handling system to prevent potential cross-contamination assessed?					
6.4.2 Controlled Environment					
6.4.2.1 For the excipient(s) undergoing evaluation, is a controlled environment necessary to avoid contamination or degradation caused by exposure to heat, air, or light, and if so, how does the degree of protection required vary, depending on the stage of the process?					
6.4.2.2 Are special environments required by any of the processes monitored to assure product quality (e.g. inert atmosphere, or protection from light)?					
6.4.2.2.1 Where an inert atmosphere is required, is the gas treated as a raw material?					
6.4.2.2.2 If interruptions in the special environment occur, is adequate evidence and appropriate rationale documented to show that such interruptions have not compromised the quality of the excipient, especially at the stage following purification of the excipient?					
6.4.3 Cleaning and Sanitary Conditions					
6.4.3.1 Has adequate cleanliness been considered in the design of excipient manufacturing facilities?					
6.4.3.2 Are buildings used in the production, processing, packaging or holding of an excipient maintained in an appropriately clean and sanitary condition according to the type of processing conducted (e.g. open/closed systems)?					

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GMP ITEM	A	NAC	NAP	NR	C/A
6.4.3.3 Where maintenance of clean and sanitary conditions is critical to excipient quality, do documented procedures assign responsibility for cleaning and sanitation, describing in sufficient detail the cleaning schedules, methods, equipment and materials to be used in cleaning the buildings and facilities?					
6.4.3.3.1 Are these procedures followed and is cleaning documented in written records?					
6.4.3.4 Is waste is segregated and disposed of in a timely and appropriate manner?					
6.4.3.4.1 If waste is not disposed of immediately, is it suitably identified and stored away from non-waste material?					
6.4.4 Pest Control					
6.4.4.1 Are buildings free from infestation by rodents, birds, insects, and other vermin?					
6.4.4.3 Are sufficient control methods in place to prevent the increase of contamination or infestation in holding areas and its spread to other areas of the plant?					
6.4.4.3.1 Do these control methods address raw materials, particularly botanicals which may contain some unavoidable contamination such as rodent or other animal filth or infestation?					
6.4.5 Lighting					
6.4.5.1 Is there adequate lighting in the facilities to provide for cleaning, maintenance and proper operations?					
6.5.6 Drainage					
6.5.6.1 In areas where the excipient is open to the environment, are there drains are of adequate size and, where connected directly to a sewer, provided with an air break or other mechanical device to prevent back siphoning?					
6.4.7 Washing and Toilet Facilities					
6.4.7.1 Are adequate personal washing facilities provided, including hot and cold water, soap or detergent, air dryers or single service towels and clean toilet facilities easily accessible to working areas?					
6.4.7.2 Are adequate facilities provided for showering and/or changing clothes, where appropriate?					
7.0 PRODUCT REALIZATION					
7.1 Planning of Product Realization					
7.1.1 Has the excipient manufacturer planned and developed the processes and controls needed for the product manufacture?					
7.1.2 Are these plans and controls appropriate to the production process, excipient specification, equipment and facilities used in the manufacture of the excipient?					
7.1.3 Were the following key aspects of the planning of a suitable process and its controls included:					
7.1.3.1 Documented testing programs for quality-critical materials including excipients that include appropriate specifications, sampling plans, test and release procedures?					
7.1.3.2 Generation and maintenance of records (see also 4.2.4) that provide evidence that these plans have been realized as intended and that enable traceability to be demonstrated (see also 7.5.3.1)?					
7.1.3.3 Provision of resources to implement these plans?					
7.1.3.4 Environmental and hygiene control programs to minimize contamination?					

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GMP ITEM	A	NAc	NAp	NR	C/A
7.2 Customer-related Processes					
7.2.1 Determination of Requirements Related to the Product					
7.2.1.1 Has the excipient manufacturer determined the excipient quality, labeling, and delivery requirements of the customer?					
7.2.1.2 Have additional requirements, whether customer specific, legal or regulatory (e.g. pharmacopoeia material and general monographs), been agreed to by both the excipient manufacturer and the customer?					
7.2.1.3 Have requirements not stated by the customer but necessary for specified or intended use, where known, been considered?					
7.2.2 Review of Requirements Related to the Product					
7.2.2.1 Have the excipient manufacturer and customer mutually agreed to the excipient requirements in 7.2.1 before supply commences?					
7.2.2.2 Does the excipient manufacturer have the facility and process capability to meet consistently the mutually agreed specifications?					
7.2.2.3 When the excipient requirements of 7.2.1 are changed, does the manufacturer conduct a repeat review and approval before supply recommences?					
7.2.3 Customer Communication					
7.2.3.1 Has the excipient manufacturer established provisions for providing accurate and pertinent communication to the customer?					
7.2.3.2 Does the excipient manufacturer notify customers of significant changes?					
7.2.3.3 Are master copies of documents such as specifications and technical reports controlled documents?					
7.2.3.4 Are there provisions for replying to customer inquiries, contracts, and order handling requirements?					
7.2.3.5 Are customer feedback and complaints documented?					
7.2.3.6 Are customers notified of significant changes (see also 4.3)?					
7.3 Design and Development					
7.3.0 If the excipient manufacturer handles requirements for ensuring control over design and development activities, do they comply with recommendations made in the requirements of ISO 9001?					
7.3.0.1 Although full GMP is not always applicable during the design and development of new excipients and/or manufacturing processes, development batches of excipients that are intended for use in drug products should be manufactured in accordance with the applicable provisions of this guide. Was this the case for any of the excipients undergoing evaluation?					

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GMP ITEM	A	N/Ac	N/AP	NR	C/A
7.4 Purchasing					
7.4.1 Purchasing Process					
7.4.1.1 Does the excipient manufacturer have a system for selecting and approving suppliers of quality-critical materials and services (e.g. subcontract manufacturers and laboratories)?					
7.4.1.2 Does the supplier approval by the quality unit require an evaluation of the supplier's quality management system, including adequate evidence that they can consistently meet agreed requirements?					
7.4.1.3 Does the excipient manufacturer require periodic audits of the supplier's manufacturing facility?					
7.4.1.4 Are records of these activities maintained by the excipient manufacturer?					
7.4.1.5 Are materials purchased against an agreed specification from approved suppliers?					
7.4.2 Purchasing Information					
7.4.2.1 Do purchasing agreements describe the material or service ordered including, where critical to excipient quality, the following:					
7.4.2.1.1 The name, type, class, style, grade, item code number or other precise identification traceable to the raw material and packaging specifications?					
7.4.2.1.2 Drawings, process requirements, inspection instructions and other relevant technical data, including requirements for approval or qualification of product, procedures, process equipment and personnel?					
7.4.2.1.3 Adherence to the appropriate sections of this guide for relevant contract manufacturers or laboratories?					
7.4.2.1.4 A statement to notify the excipient manufacturer of significant changes in quality-critical raw materials?					
7.4.3 Verification of Purchased Product					
7.4.3.1 Are there procedures for the approval and release of quality-critical material?					
7.4.3.2 Upon receipt, are quality-critical materials placed in quarantine and not be used prior to acceptance?					
7.4.3.3 Is the quarantined of quality-critical material established with suitable identifying labels, signs and/or other manual documentation systems?					
7.4.3.4 When quarantine and stock control are managed with computer systems in lieu of a physical stock control, are there system controls in place to prevent the use of unreleased material?					
7.4.3.5 For material supplied by pipeline, where quarantine may not be feasible, has the excipient manufacturer established an agreement with the supplier so that they are notified of material that does not meet specification?					
7.4.3.6 Are sampling activities conducted under defined conditions, in accordance with a defined sampling method and using procedures designed to prevent contamination and cross-contamination?					
7.4.3.7 Are quality-critical materials used in the manufacture of an excipient tested or otherwise verified prior to use?					
7.4.3.8 Is Certificate of Analysis (COA) required from the suppliers of quality-critical material?					
7.4.3.9 Are supplier's COAs checked and is an identification test performed?					
7.4.3.10 Are testing schedules organized to separate those tests that are routine from those that are performed infrequently or only for new suppliers?					

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7.4.3.11 Does the excipient manufacturer ensure that for bulk deliveries additional controls are place to assure material purity and free from contamination?					
7.5 Production and Service Provision					
7.5.1 Control of Production and Service Provision					
7.5.1.0 Are all production activities are carried out under controlled conditions (also see 7.1)?					
7.5.1.1 Production Instructions and Records					
7.5.1.1.1 Are there established production instructions and records to deal with either batch production or continuous production processes?					
7.5.1.1.2 Is there a controlled document that describes how the excipient is produced (e.g. master production instructions, master production and control records, process definitions, etc.)?					
7.5.1.1.3 For batch processes, is an accurate reproduction of the appropriate master product instructions issued to the production area?					
7.5.1.1.4 For continuous processes, is there a current established processing log available?					
7.5.1.1.5 For batch processes, are records available for each batch of excipient produced, which include complete information relating to the production and control of each batch?					
7.5.1.1.6 For continuous processes, are batches and its records that defined (e.g. based on a defined quantity such as time or size)?					
7.5.1.1.7 Are batch production and control records (which may be in different locations) readily retrievable?					
7.5.1.1.8 Do records for both batch and continuous processing, where critical to excipient quality, include the following:					
7.5.1.1.8.1 Date/time each step was completed or date/time log of key parameters?					
7.5.1.1.8.2 Identification of persons performing and directly supervising or checking each significant step, operation or control parameter?					
7.5.1.1.8.3 Identification of major equipment and lines used?					
7.5.1.1.8.4 Material inputs to enable traceability, for example, batch number and quantities of raw material/intermediate, time it was added, etc.?					
7.5.1.1.8.5 In-process and laboratory control results?					
7.5.1.1.8.6 The quantity produced for the defined batch and a statement of the percentage of theoretical yield, unless not quantifiable (e.g. as in some continuous processes)?					
7.5.1.1.8.7 Inspection of the packaging and labeling area before and after use?					
7.5.1.1.8.8 Labeling control records?					
7.5.1.1.8.9 Description of excipient product containers and closures?					
7.5.1.1.8.10 Description of sampling performed?					
7.5.1.1.8.11 Failures, deviations and their investigations?					
7.5.1.1.8.12 Results of final product inspection?					
7.5.1.2 Equipment Cleaning					
7.5.1.2.1 Has the manufacturer designed and justified cleaning and sanitization procedures and provided evidence of their effectiveness?					
7.5.1.2.2 In multi-purpose plants, has the excipient manufacturer employed the use of the “model product approach” (groups of product of similar type) in justifying a suitable procedure?					
7.5.1.2.3 Are cleaning and sanitization procedures documented?					
7.5.1.2.4 Do cleaning procedures contain sufficient detail to allow operators to clean each type of equipment in a reproducible and effective manner?					

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7.5.1.2.5 Is there a record confirming that these cleaning procedures have been followed?					
7.5.1.2.6 Are equipment and utensils cleaned and sanitized, where critical to excipient quality, and at appropriate intervals to prevent contamination and cross-contamination of the excipient?					
7.5.1.2.7 Is the cleaning status of equipment recorded appropriately?					
7.5.1.2.8 Where multi-purpose equipment is in use, is there a system to determine previous usage when investigating cross-contamination or the possibility of such contamination (see also 7.5.1.7)?					
7.5.1.2.9 For products that leave residues that cannot be effectively removed, are dedicated equipment designated for their production?					
7.5.1.2.10 For continuous processing, has the frequency of equipment cleaning been determined and justified?					
7.5.1.3 Recovery of Solvents, Mother Liquors and Second Crop Crystallization					
7.5.1.3.1 Where solvents are recovered and reused in the same process or different processes, is there a system to ensure that they meet appropriate standards prior to reuse or mixing with other approved material?					
7.5.1.3.2 Where mother liquors or filtrates containing recoverable amounts of excipient, reactants, or intermediates are reused, are such processes documented in the production records or logs to enable traceability?					
7.5.1.4 In-process Blending or Mixing					
7.5.1.4.1 Where in-process blending or mixing to assure batch uniformity or to facilitate processing is performed, is it done in a controlled and documented manner?					
7.5.1.4.2 If the intent of the operation is to ensure batch uniformity, is it performed in a manner to assure homogenous mixing of materials to the extent feasible and is it reproducible from batch to batch?					
7.5.1.5 In-process Control					
7.5.1.5.1 Is in-process inspection and testing performed based upon monitoring the process or actual sample analysis at defined locations and times?					
7.5.1.5.2 Are sampling methods documented to ensure that the sample is representative and clearly labeled?					
7.5.1.5.3 Are in-process samples not returned to production for incorporation into the final batch?					
7.5.1.5.4 Are the results of in-process tests recorded and conform to established process parameters or acceptable tolerances?					
7.5.1.5.5 Do work instructions define the procedure to follow and how to utilize the inspection and test data to control the process?					
7.5.1.5.6 Are there defined actions to be taken when the results are outside specified limits?					
7.5.1.5.7 Where approval to continue with the process is issued within the production department, are the specified tests performed by trained personnel and are the results recorded?					
7.5.1.6 Packaging and Labeling					
7.5.1.6.1 Are procedures employed to protect the quality and purity of the excipient when it is packaged and to assure that the correct label is applied to all containers?					
7.5.1.6.2 Are packaging and labeling operations designed to prevent mix-ups?					

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7.5.1.6.3 Are procedures implemented to ensure that the correct labels are printed and issued and that the labels contain the correct information?					
7.5.1.6.4 Does the procedure also specify that excess labels are immediately destroyed, or returned to controlled storage?					
7.5.1.6.5 Are excess labels bearing batch numbers destroyed and documented?					
7.5.1.6.6 Are packaging and labeling facilities inspected immediately before use to ensure that materials that are not required for the next packaging operation have been removed?					
7.5.1.6.7 Where excipients are labeled on the packaging line, packaged in preprinted bags or bulk-shipped in tank cars, is there documentation of the system used to satisfy the intent of the aforementioned procedures?					
7.5.1.7 Records of Equipment Use					
7.5.1.7.1 Are records of quality-critical equipment use retained?					
7.5.1.7.2 Do the records allow the sequence of cleaning, maintenance, and production activities to be determined?					
7.5.2 Validation of Processes for Production and Service Provision					
7.5.2.1 To assure product quality, since testing alone is not sufficient to reveal variations that may have occurred, has adequate design and control of the manufacturing process been assessed?					
7.5.2.1.1 Is each step of the manufacturing process controlled to the extent necessary to ensure that the excipient meets established specifications?					
7.2.2.2 Has process validation been performed to ensure that quality assurance goals are met?					
7.5.2.2.1 Are process reactions, operating parameters, purification steps, impurities, and key tests needed for process control documented, thus providing the basis for validation?					
7.5.2.3 Although the full validation program that is typically performed in the pharmaceutical industry may not always be carried out by the excipient manufacturer, has the excipient manufacturer demonstrated the consistent operation of each manufacturing process (e.g. through process capability studies, development and scale-up reports, etc.)?					
7.5.3 Identification and Traceability					
7.5.3.1 Traceability					
7.5.3.1.1 Are quality-critical items (e.g. raw materials, packaging materials, intermediates, and finished excipients) clearly identified and traceable through records?					
7.5.3.1.1.1 Do the records allow traceability of the excipient both upstream and downstream?					
7.5.3.1.1.2 Is the identification of raw materials used in batch production processes traceable through the batch numbering system or other appropriate system?					
7.5.3.1.1.3 Is the identification of raw materials used in excipients produced by continuous processing indicated by the timeframe during which a particular batch of raw material was processed through the plant?					
7.5.3.1.2 For raw materials including solvents stored in bulk tanks or other large containers, for which precise separation is difficult, is the use of such material documented in production records?					
7.5.3.2 Inspection and Test Status					
7.5.3.2.1 Is there a system to identify the inspection status of quality-critical items including raw materials, packaging materials, intermediates, and finished excipients?					
7.5.3.2.1.1 Whilst storing materials in identified locations is preferred, any means that clearly identifies the test status is satisfactory. Continuously-fed materials may need special consideration in order to satisfy these requirements. What system is used and is it acceptable?					

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7.5.3.3 Labeling					
7.5.3.3.1 What national/international regulatory requirements, including transportation and safety measures are the labeling for excipient packages subject to?					
7.5.3.3.2 As a minimum, labels should include the name of the excipient and grade if applicable; the excipient manufacturer's and/or distributor's name; the batch number from which the complete batch history can be determined; special storage conditions, if applicable.					
7.5.4 Customer Property					
7.5.4.1 Has the excipient manufacturer established and maintained procedures for verification, storage, and maintenance of customer-supplied materials intended for incorporation into the customer's excipient?					
7.5.4.2 Although verification by the excipient manufacturer does not relieve the customer of the responsibility to provide an acceptable material, material that is lost, damaged or is otherwise unsuitable for use should be recorded and reported to the customer. For cases such as this, are there procedures in place for acceptable disposition and replacement of the material?					
7.5.4.3 Has the excipient manufacturer made provisions to protect other real and intellectual property that is provided by the customer (e.g. test equipment, test methods and specifications)?					
7.5.5 Preservation of Product					
7.5.5.1 Handling, Storage and Preservation					
7.5.5.1.1 Are excipients, intermediates, and raw materials handled and stored under appropriate conditions of temperature, humidity, and light so that their identity, quality, and purity are not affected?					
7.5.5.1.2 For outdoor storage of raw materials (e.g. acids, other corrosive substances or explosive materials) or excipients, are materials stored in containers that give suitable protection against deterioration or contamination of their contents, do identifying labels remain legible and are containers adequately cleaned prior to opening and use?					
7.5.5.1.3 Are records of storage of raw materials maintained by the manufacturer, especially if critical for continuing conformance of material to specification?					
7.5.5.2 Packaging Systems					
7.5.5.2.1 Does the excipient manufacturer's packaging system include the following features:					
7.5.5.2.1.1 Documented specifications and examination or testing methods?					
7.5.5.2.1.2 Cleaning procedures where containers are reused?					
7.5.5.2.1.3 Tamper-evident seals?					
7.5.5.2.1.4 Containers that provide adequate protection against deterioration or contamination of the excipient during transportation and recommended storage?					
7.5.5.2.1.5 Containers that do not interact with or contaminate the excipient?					
7.5.5.2.1.6 Storage and handling procedures which protect containers and closures and minimize the risk of contamination, damage or deterioration and which will avoid mix-ups (e.g. between containers that have different specifications but are similar in appearance)?					
7.5.5.2.2 If returnable excipient containers are re-used, are previous labeling removed or defaced?					
7.5.5.2.3 If the containers are repetitively used solely for the same excipient, are previous batch numbers or the entire label removed or completely obliterated?					
7.5.5.2 Delivery and Distribution					
7.5.5.2.1 Identification and traceability of quality-critical aspects are required of excipient manufacturers. Does the excipient manufacturer keep distribution records of excipient shipments?					
7.5.5.2.2 Do these records identify, by excipient batch, where and to whom the excipient was shipped, the amount shipped and the date of shipment so as to facilitate retrieval if necessary?					
7.5.5.2.3 Where excipients are handled by a series of different distributors, is it possible to trace them back to the original manufacturer and not just to the previous supplier?					
7.5.5.2.4 Does the manufacturer maintain the integrity and the quality of the product after final inspection and test?					

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7.5.5.2.4.1 Where contractually specified, does this protection extended to include delivery to the final destination?					
7.5.5.2.5 Are excipients supplied within their expiry and/or retest period?					
7.6 Control of Measuring and Monitoring Devices					
7.6.1 Are measuring and test equipment, including computerized systems, identified as being quality-critical calibrated and maintained?					
7.6.1.1 Does this include in-process instruments as well as test equipment used in the laboratory?					
7.6.2 Does the control program include the standardization or calibration of instruments and equipment at suitable intervals in accordance with an established documented program?					
7.6.3 Does the program contain specific directions, schedules, limits for accuracy and precision, and provisions for remedial action in the event that accuracy and/or precision limits are not met?					
7.6.4 Are calibration standards traceable to recognized national or compendial standards as appropriate?					
7.6.5 Are instruments and equipment not meeting established specifications not used, and is an investigation conducted to determine the validity of the previous results since the last successful calibration?					
7.6.6 Is the current calibration status of quality-critical equipment known and verifiable to users?					
8.0 MEASUREMENT, ANALYSIS AND IMPROVEMENT					
8.1 General					
8.1.1 Has the organization established a plan and implemented the monitoring, measurement and improvement activities required to demonstrate conformity of the excipient to customer requirements and to ensure conformity of the quality management system to this guide?					
8.1.2 Has the organization evaluated opportunities for improvements through the measurement and analysis of product and process trends?					
8.2 Monitoring and Measurement					
8.2.1 Customer Satisfaction					
8.2.1.1 Has the Excipient Manufacturer established measurement activities to assess customer satisfaction?					
8.2.1.2 Do measurement activities include customer complaints, return of excipients and customer feed back?					
8.2.1.3 Is this information used to drive activities that strive to continuously improve customer satisfaction?					
8.2.2 Internal Audits					
8.2.2.1 Is there a comprehensive system of planned and documented internal quality audits?					
8.2.2.2 Do the internal audits determine whether quality activities comply with planned arrangements and the effectiveness of the quality management system?					
8.2.2.3 Are internal audits scheduled on the basis of the status and importance of the activity?					
8.2.2.4 Are audits and follow-up actions carried out in accordance with documented procedures?					
8.2.2.5 Are audit results documented and discussed with management personnel having responsibility in the area audited?					
8.2.2.6 Do management personnel responsible for the area audited initiated take corrective action on the nonconformities found?					
8.2.3 Monitoring and Measurement of Processes					
8.2.3.1 Has the manufacturer identified the tests and measurements necessary to adequately control manufacturing and quality management system processes?					
8.2.3.2 Where critical to excipient quality, are techniques established to verify that the processes are under control?					
8.2.3.3 Is appropriate corrective action taken to ensure that excipients meet requirements when deviation from planned results occur?					
8.2.3.4 Are periodic reviews of key indicators (e.g. process quality attributes and process failures) conducted to assess the need for improvements?					

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8.2.4 Monitoring and Measurement of Product					
8.2.4.0.1 Has the manufacturer established test methods and procedures to ensure that the excipient consistently meet established specifications?					
8.2.4.0.2 Are analytical procedures fit for purpose?					
8.2.4.0.3 Does the manufacturer claim that their excipient is in compliance with a pharmacopoeia or an official compendium?					
8.2.4.0.3.1 If so, are compendial test procedures followed?					
8.2.4.0.3.2 If so, are non-compendial analytical tests demonstrated to be equivalent to those in the compendia?					
8.2.4.0.4.3 Does the excipient comply with applicable general chapters and notices?					
8.2.4.0.5 Does the manufacturer claim that excipient complies with another standard, other than an official standard, and if so what standard is it?					
8.2.4.1 Laboratory Controls					
8.2.4.1.1 Do laboratory controls include complete data derived from tests necessary to ensure conformance with specifications and standards, and include:					
8.2.4.1.1.1 A description of the sample received for testing together with the material name, batch number or other distinctive code and date sample was taken?					
8.2.4.1.1.2 A statement referencing each test method used?					
8.2.4.1.1.3 A record of raw data secured during each test including graphs, chromatogram, charts and spectra from laboratory instrumentation, identified to show the specific material and batch tested?					
8.2.4.1.1.4 A record of calculations performed in connection with the test?					
8.2.4.1.1.5 Test results and how they compare with established specifications?					
8.2.4.1.1.6 A record of the person who performed each test and the date(s) the tests were performed?					
8.2.4.1.2 Is there a documented procedure for the preparation of laboratory reagents and solutions?					
8.2.4.1.3 Are purchased reagents and solutions labeled with the proper name, concentration and expiry date?					
8.2.4.1.4 Are records maintained for the preparation of solutions, including the name of the solution, date of preparation and quantities of material used?					
8.2.4.1.5 Are volumetric solutions standardized according to an internal method or by using a recognized standard?					
8.2.4.1.6 Are records of the standardization maintained?					
8.2.4.1.7 Are primary reference reagents and standards appropriately stored and tested upon receipt, if no certificate of analysis is received from the supplier?					
8.2.4.1.8 Are secondary reference standards appropriately prepared, identified, tested, approved, and stored?					
8.2.4.1.9 Are there documented procedures for the qualification of secondary reference standards against primary reference standards?					
8.2.4.1.10 Are re-evaluation periods defined for secondary reference standards, and is each batch periodically requalified in accordance with a documented protocol or procedure?					
8.2.4.2 Finished Excipient Testing and Release					
8.2.4.2.1 Is finished excipient testing conducted on each batch to ensure that the excipient conforms to documented specifications?					
8.2.4.2.2 Is there a procedure to ensure that appropriate manufacturing documentation, in addition to the test results, is evaluated prior to release of the finished excipient?					
8.2.4.2.3 Is the quality unit responsible for the release of the finished excipient?					
8.2.4.2.4 For excipients produced by continuous processes, is assurance that the excipient conforms to documented specifications achieved through the results of in-process testing or other process control records?					
8.2.4.3 Out-of-Specification Test Results					
8.2.4.3.1 Are Out-of-specification (OOS) test results investigated and documented according to a documented procedure?					
8.2.4.3.2 Are retest sample results only used to replace the original result if it is demonstrated that the original result was erroneous based on a documented investigation?					

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8.2.4.3.3 Does the OOS procedure define which statistical techniques are to be used and under what circumstances?					
8.2.4.3.3.1 When statistical analysis is used, are both the original and retest data used?					
8.2.4.3.4 Do these same principles apply when the sample is suspected of not being representative of the material from which it was taken?					
8.2.4.4 Retained Samples					
8.2.4.4.1 Where practical, is a representative sample of each batch of excipient retained?					
8.2.4.4.2 Is the retention period appropriate to the expiry or re-evaluation date?					
8.2.4.4.3 Are the retained samples stored and maintained in such manner that they are readily retrievable in facilities that provide a suitable environment?					
8.2.4.4.4 Is the retain sample size is at least twice the amount required to perform complete specification testing?					
8.2.4.5 Certificate of Analysis					
8.2.4.5.1 Does the organization provide a certificate of analysis (CoA) to the required specification for each batch of excipient?					
8.2.4.5.2 Do the contents of the CoA follow the guidance provided in IPEC-Americas Certificate of Analysis Guide for Bulk Pharmaceutical Excipients?					
8.2.4.6 Impurities					
8.2.4.6.1 Where possible, does the manufacturer identify and set appropriate limits for impurities?					
8.2.4.6.2 Are the limits based upon appropriate safety data, limits as described in official compendia or other requirements and sound GMP considerations?					
8.2.4.6.3 Are manufacturing processes adequately controlled so that impurities do not exceed established limits?					
8.2.4.6.4 Does the excipient specification include tests and limits for solvent residues, especially in cases where the excipient is extracted from or purified using organic solvents and the solvents are removed by drying?					
8.2.4.7 Stability					
8.2.4.7.1 Has the excipient been on the market for a long time?					
8.2.4.7.2 Is historical data used to indicate stability?					
8.2.4.7.3 Does the excipient manufacturer have a documented testing and/or evaluation program designed to assess the stability characteristics of the excipient?					
8.2.4.7.4 Are the results of stability testing and/or evaluation used to determine appropriate storage conditions and retest or expiry dates?					
8.2.4.7.5 Does the stability testing program included the following:					
8.2.4.7.5.1 The number of batches, sample sizes and test intervals?					
8.2.4.7.5.2 Storage conditions for samples retained for testing?					
8.2.4.7.5.3 Suitable stability-indicating test methods?					
8.2.4.7.5.4 Storage of the excipient in containers that simulate the market container, where possible?					
8.2.4.7.6 Is the stability of excipients affected by undetected changes in raw materials or subtle changes in manufacturing procedures or storage conditions?					
8.2.4.7.7. Is the excipient shipped in a variety of packaging types that can affect their stability (e.g. plastic or glass bottles, metal or plastic drums, bags, tank cars or other bulk containers, etc.)?					
8.2.4.7.8 Is the excipient available in different grades (e.g. various molecular weights of a polymer or different monomer ratios, different particle sizes, bulk densities, etc.) or mixtures of other excipients?					
8.2.4.7.8.1 For excipients that are similar to other excipients within a product group, with only minor quantitative differences of some of the components or other minor but significant variations, is a "model product" approach used to assess the stability of these similar excipients?					
8.2.4.7.8.2 Do the stability studies of this type involve selection of several "model products" that would be expected to simulate the stability of the product group being assessed?					
8.2.4.7.8.3 Is the selection based on scientifically sound and adequate to be able to determine a theoretical stability for similar excipients?					

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8.2.3.8 Expiry/Retest Periods					
8.2.3.8.1 Is an expiry or retest period assigned to each excipient and communicated to the customer?					
8.3 Control of Nonconforming Product					
8.3.0.1 Is raw material, intermediate or finished excipient found not to meet its specification clearly identified and controlled to prevent inadvertent use or release for sale?					
8.3.0.2 Is a record of nonconforming product maintained?					
8.3.0.3 Are incidences of non-conformance investigated to identify the cause?					
8.3.0.4 Are the investigations documented and action taken to prevent recurrence?					
8.3.0.5 Is there a documented procedure defining how the retrieval of an excipient from distribution should be conducted and recorded?					
8.3.0.6 Is there a procedure for the evaluation and subsequent disposition of nonconforming products?					
8.3.0.7 Are nonconforming product reviewed in accordance with documented procedures to determine if it may be: reprocessed/reworked to meet the specified requirements; accepted by the customer with their agreement; re-graded for other applications; or destroyed?					
8.3.1 Reprocessing					
8.3.1.1 Is there an established procedure for reprocessing (repetition of an activity that is a normal part of the manufacturing process)?					
8.3.1.2 Does reprocessing occur only when it has already been documented that the excipient may be made in that manner?					
8.3.1.2.1 When reprocessing has not been documented as being feasible, is the guidance for reworking followed instead?					
8.3.2 Reworking					
8.3.2.1 Is there an established procedure for reworking (an activity that is not a normal part of the manufacturing process)?					
8.3.2.2 Is reworking only conducted following a documented review of risk to the excipient quality and approval by the quality unit?					
8.3.2.3 When performing risk assessment is consideration is given to the following:					
8.3.2.3.1 New impurities that may be introduced as a result of reworking?					
8.3.2.3.2 Additional testing to control the reworking?					
8.3.2.3.3 Records and traceability to the original batches?					
8.3.2.3.4 Suitable acceptance criteria for the reworked excipient?					
8.3.2.3.5 Impact on stability or the validity of the re-evaluation interval?					
8.3.2.3.6 Performance of the excipient?					
8.3.2.4 When the need to rework an excipient is identified, is an investigation and evaluation of the cause required?					
8.3.2.5 Is the equivalence of the quality of the reworked material to original material evaluated and documented to ensure that the batch will conform to established specifications and characteristics?					
8.3.2.6 Are batches of excipients that do not conform to specifications individually <u>not</u> blended with other batches that do not conform in an attempt to hide adulterated or sub-standard material?					

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