

NOTICE

This manual provides information to drug product manufacturers who wish to participate in the United States Pharmacopeia's Excipient Supplier Qualification Program (USP Excipient SQP or "Program").

The Excipient Supplier Qualification Program involves GMP auditing and testing for conformity. USP's intention is to provide guidance and direction to manufacturers of excipients and users of excipients used in the pharmaceutical industry to assist them in complying with the USP Excipient SQP requirements. USP considers this a cooperative effort between USP and the manufacturers and the users. USP encourages manufacturers and users of excipients to provide input, based on their needs and experience, to help shape the future direction and requirements of the USP Excipient SQP. Barring safety concerns or other special circumstances, USP maintains the confidentiality of information gained through the qualification process in accordance with the provisions of the Program Agreement.

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1. OVERVIEW

The United States Pharmacopeia's Excipient Supplier Qualification Program (USP Excipient SQP) is a public health program of the United States Pharmacopeia (USP). Participation is voluntary and open to pharmaceutical companies that use excipients and require qualification of their excipient vendors.

The USP Excipient SQP covers excipients used in the manufacture of pharmaceutical products.

The USP Excipient SQP includes:

- Evaluation of supplier's quality systems through audit of each manufacturing site for compliance with Good Manufacturing Practices (e.g., USP General Chapter <1078> *Good Manufacturing Practices for Bulk Pharmaceutical Excipients*, International Pharmaceutical Excipients Council's IPEC/POG *GMP Guide for Pharmaceutical Excipients*)
- Testing for compliance with *USP-NF*, *EP* and/or *JP* monographs, as applicable. In addition, testing for the drug product manufacturer's additional specifications, if any.
- Laboratory testing of excipient samples from selected batches for compliance with the participant's specification for the excipient.
- Issuance of a letter to the participant indicating the supplier's USP Excipient SQP qualification status

Successful qualification of an excipient supplier provides assurance that:

- The supplier's quality system helps to ensure that the excipient being supplied meets its specification for identification, strength, purity, and quality, and is consistent in quality from batch to batch.
- The excipient is prepared under accepted good manufacturing practices.
- The excipient meets compendial and/or drug product manufacturer's own purchase specification, including requirements for acceptable limits of contaminants and impurities.

Thus, the USP Excipient SQP offers users of excipients a trusted means of qualifying the suppliers of excipients used in the manufacture of drug products.

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Since 1820, the **United States Pharmacopeia (USP)** has been a trusted and recognized source of standards for the identification, strength, quality, and purity of medicines, dietary supplements, and related products. These standards are developed by a unique process involving all interested parties and are accepted by many countries worldwide.

USP is a non-governmental, not-for-profit organization with a mission to promote quality in public health. Scientific experts and other individuals representing numerous fields including pharmacy, medicine, and other health care professions; academia; the U.S. Government; the pharmaceutical industry; the dietary supplement industry; and consumer organizations, volunteer their efforts to support USP's work.

The USP Excipient SQP is a natural progression of USP's long history of establishing officially recognized public standards for drug substances, drug products, biologics, biotechnologically derived products, medical devices, dietary supplements, and excipients. Please visit www.usp.org to learn more about USP.

2. CRITERIA FOR PARTICIPATION

Drug product manufacturers participating in the USP Excipient SQP agree to:

- Complete the Program Agreement in cooperation and collaboration with the excipient supplier(s)
- Work with the excipient supplier(s) to eliminate the need for USP to sign a confidentiality agreement with the excipient supplier(s).
- Work with the excipient supplier(s) to submit any requested data and documentation.
- Collaborate with the excipient supplier(s) to subject the supplier's excipient(s) and facilities to all testing and audits specified in the Program.
- Abide by the decisions made in accordance with the rules and requirements of the USP Excipient SQP.
- Operate in accordance with the provisions of relevant federal regulations.
- Pay all fees required by USP agreements or by documents executed between the drug product manufacturer and USP.

3. REQUIRED PROCESS AND SUBMISSIONS

Please note that all submissions to the Program must be in English. Translations of documents not originally created in English must be certified by the participant or participant's representative.

Excipient manufacturer that wish to participate in the USP Excipient SQP shall:

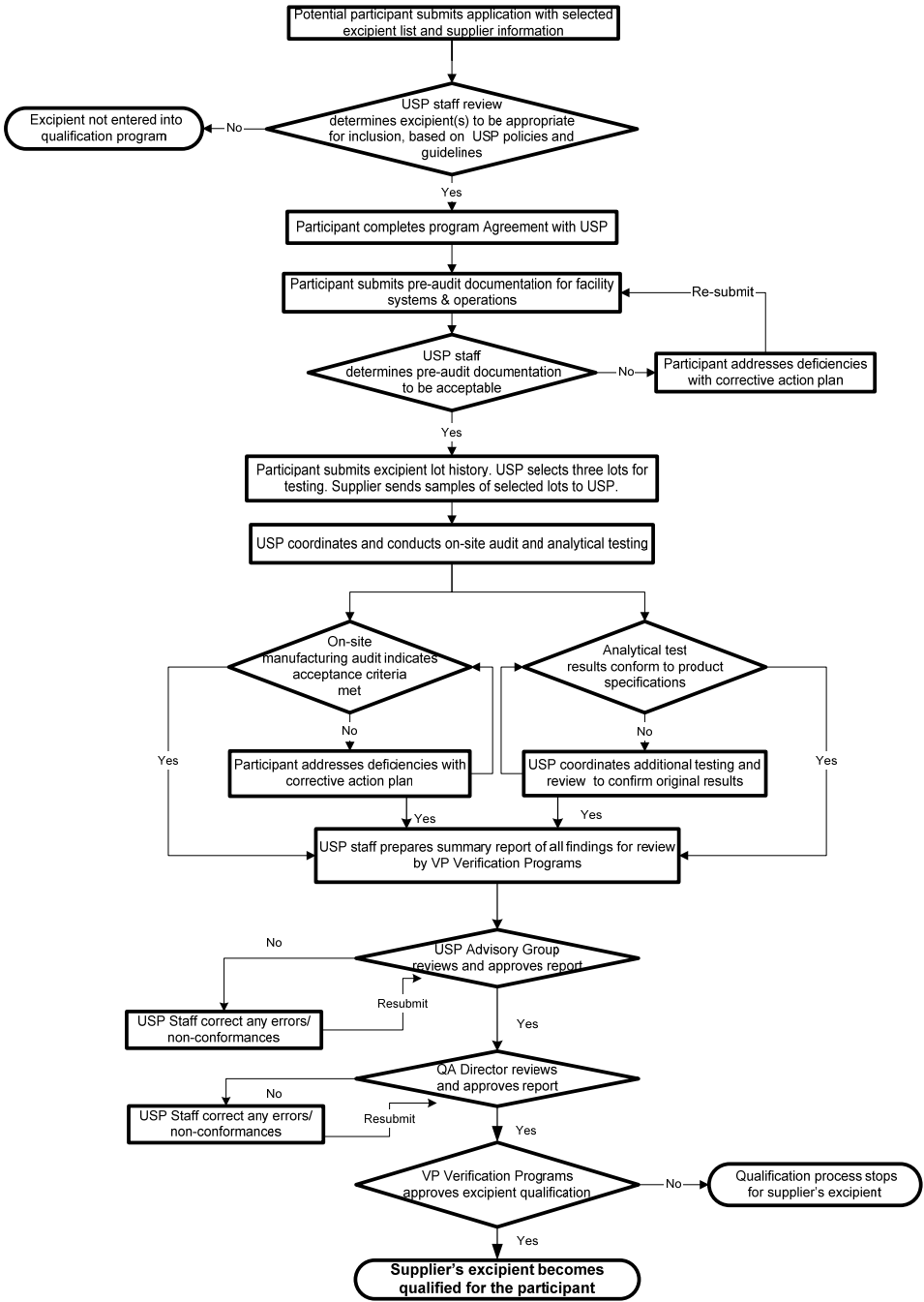
- Appoint a duly authorized representative to execute a Program Agreement.
- Provide the name and address of the supplier(s) of the excipient for which qualification is sought, with batch history for not less than ten (10) batches of the excipient or batches manufactured dating back one year (if available), whichever comes first for the excipient, manufactured under the supplier's current quality system.
- Work with the supplier(s) to provide USP Excipient SQP with representative sample aliquots of the excipient(s) as specified by USP Excipient SQP staff.
- Work with the supplier(s) to submit the following documentation as described in this Manual for Participants:
 1. Pre-audit documentation (see Forms and Checklists, section 14)
 2. 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 demonstrating that the article is safe for human use must be included in the submitted documentation. These data may be reviewed by the USP Expert Committee.

¹ 802 country: A country that is recognized under section 802(b)(1)(A) of the Federal Food, Drug, and Cosmetic Act and to which a drug or device may be exported, without having the drug or device approved by the U.S. Food and Drug Administration, if the drug or device complies with the laws of that country and has valid marketing authorization by the appropriate authority. 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.

3. Excipient release: specification (physical, chemical, and microbiological tests, analytical procedures, and acceptance criteria) and test results for the three batches of excipient (s) selected for testing in USP laboratories.
4. Excipient in-line, on-line, and at-line tests when used for release.
5. An executed batch record for one of the three batches of the excipient (s) selected for testing in USP laboratories. Under some circumstances, the USP auditor may be asked to review the executed batch sheet during on-site audit.
6. Packaging and labeling records for the three batches of the excipient(s) selected for testing in USP laboratories.

4. PROCESS FLOW CHART

EXCIPIENT SQP PROCESS



5.

EXCIPIENT ACCEPTANCE INTO USP EXCIPIENT SQP

Upon completion of the Program Agreement, the drug product manufacturer submits to USP Excipient SQP a list of excipients for which supplier qualification is sought. USP Excipient SQP 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 Excipient SQP the excipient batch history (batch number, description of the batch number coding system, date of manufacture, manufacturing facility, and batch size) for not less than ten (10) batches of the excipients or batches manufactured dating back one year (if available), whichever comes first for the excipient, for which supplier qualification is sought that have been manufactured under the supplier's current quality systems. Also, the participant submits the list of lots recalled, if any, in the past five years for the excipient(s) under consideration.

Excipients which are used in FDA approved drug products or in drug products approved by an 802 country are on the current "Approved" list for inclusion in the USP Excipient SQP.

All other excipients will require an evaluation, with the established criteria for inclusion, before the excipient can be included in the USP Excipient SQP.

6. EVALUATION OF PRE-AUDIT DOCUMENTATION

The Checklist for Pre-Audit Documentation (see Forms and Checklists, section 14) is used by USP Excipient SQP as a tool to ascertain information about the excipient supplier, its quality systems, and critical manufacturing information.

The supplier, working with the Participant, should provide the information listed on the Checklist for Pre-Audit Documentation to USP Excipient SQP. Upon receipt of the form and information, USP Excipient SQP staff will perform a preliminary review of the information. If additional information is required, USP Excipient SQP staff will inform the excipient supplier; such information should be submitted within 30 calendar days.

Note that the requested information must be submitted in the format indicated on the Checklist for Pre-Audit Documentation (section 14). The requested information should be submitted electronically. If electronic submission is not feasible, then the information may be submitted in a three ring binder. Complete documentation must be received before the review and audit process can begin.

In evaluating the Checklist for Pre-Audit Documentation, the absence of any of the following listed elements will be determined as deficiencies that will exclude the excipient supplier from consideration for qualification until the deficiencies are corrected:

- Plant layout
- Process flow diagram
- Organizational chart
- Qualification of personnel
- Quality manual
- Control of document SOP
- Control of records SOP
- Change control SOP
- Personnel training program
- Personnel hygiene SOP
- List of equipment and qualification status
- List of utilities
- Water systems qualification & maintenance document
- Air handling unit (AHU) qualification and maintenance document
- Specification of excipient
- Labeling and packaging details

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- Quality complaint and recalls
- Internal audit SOP
- OOS investigation SOP
- Stability study SOP
- Assigning expiry and retest SOP
- Retention sample SOP
- Control of non-conforming product SOP
- Rejection, reprocessing and reworking SOP
- Product review SOP
- Process capability study
- Corrective and Preventive action SOP

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

Deficiencies, if any, will be noted, and provided to the supplier. The supplier should develop a corrective action plan within 30 calendar days of receipt of the notification. USP Excipient SQP 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 Excipient SQP, the qualification process will proceed. If the excipient supplier fails to develop and implement corrective action, the qualification process will be discontinued.

7. SUBMISSION OF EXCIPIENT SAMPLES

For a supplier for which a drug product manufacturer is seeking qualification, USP Excipient SQP will select the batches to be subjected to testing during the qualification process. This decision will be based in part on the batch history for the excipients and the availability of the excipient batches for sampling. The batches selected will be from those manufactured on the regular commercial scale. No batches manufactured under pilot scale or R & D scale will be accepted.

USP Excipient SQP will select, at minimum, three excipient batches for each excipient for which qualification of the supplier is being sought.

USP Excipient SQP will request that the excipient manufacturer obtain or arrange with the excipient supplier to provide representative sample aliquots of the excipient batches and ship them via the most expedient and appropriate courier services to the testing site identified by USP Excipient SQP. Alternatively, USP Excipient SQP may decide to send a USP Excipient SQP representative to observe the sampling.

Excipient batches should be sampled according to the supplier'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, at minimum, with the following information:

- Company Name
- Excipient Name
- Excipient Item Code Number
- Excipient Batch Number
- Date Sampled
- Sampler's Initials
- Quantity of Excipient

The supplier may be required to send sufficient quantity of samples, divided into two separate container closure systems and labeled appropriately as indicated above, for chemical and microbiological analysis.

8. TESTING OF EXCIPIENT SAMPLES

Excipients will be tested for critical quality attributes and include both chemical and microbiological tests, as determined by USP Excipient SQP to evaluate the quality of the excipient and its conformance to the supplier's specification and certificate of analysis, as well as to USP, EP and JP compendia, and the drug product manufacturer's specifications, where applicable. (See USP General Chapter <1080> Bulk Pharmaceutical Excipients – Certificate of Analysis.)

Please refer to section 9, "SPECIFICATIONS FOR 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 testing 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 the acceptance criteria provided by the excipient supplier.

If the test data obtained conform to the acceptance criteria and there are no other issues arising from the test results, USP Excipient SQP will proceed with the qualification process.

If the test data obtained do not conform to the acceptance criteria or if there are other issues arising from the test results, USP Excipient SQP will reevaluate 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 requested 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, the reanalyzed results will be averaged and reported.

In the case of nonconforming results, in which there is no determinant error, the laboratory will be requested to reanalyze the original sample, if possible, in duplicate, along with a newly submitted sample of the excipient batch, 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.

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

9. SPECIFICATIONS FOR EXCIPIENT

A specification is defined as the list of tests, analytical test procedures, and acceptance criteria that define the standard of quality for a material. 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 an excipient should conform in order 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 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 its shelf life or retest date in order to ensure that the excipient will remain within its acceptance criteria throughout its shelf life or retest date. Specifications for key intermediates, release, and shelf-life of the excipient will be reviewed during the on site audit.

The following "Universal" tests are considered generally applicable to excipients:

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

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

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

(4) Foreign Substances and Impurities: Tests should be provided for the presence of foreign substances and impurities, to limit such substances to amounts that are unobjectionable under the conditions in which the excipient is to be employed. Foreign substances and impurities can arise from raw materials, 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.

(a) 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.

(b) 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).

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

The applicability of the following "Specified" tests depends on the nature of the excipient and its intended use in drug products.

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

(6) 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.

(7) 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.

(8) 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.

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

(10) 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, one should consult *European Pharmacopoeia (EP)* General Chapter 5.2.8, "Minimizing the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Medicinal Products", and the U.S. Department of

Agriculture, Animal and Plant Health Inspection Service (APHIS) Federal Register: November 4, 2003, Volume 68, Number 213 (Proposed rules) 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.

(11) Microbial Limits: There may be a need to specify the total count of aerobic microorganisms, 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., USP-NF General Chapter <61> *Microbial Limit Tests*).

For questions or clarification regarding specifications for raw materials and/or excipients, please contact USP Excipient SQP staff at 301-816-8273.

10. ON-SITE AUDIT CRITERIA

USP staff auditors and/or approved contract auditors perform the on-site audit of the supplier's facilities and operations. In general, suppliers will contact internal audits on annual basis after successfully completing all aspects of the Program. USP may conduct additional on-site audits on a for-cause basis, in response to a major change, or as a follow-up to the initial audit when Action Level 1 deficiencies are noted (see section 11, USP EXCIPIENT SQP REPORT OF FINDINGS).

In consultation with the drug product manufacturer, the audit may be performed with notice at a date and time mutually agreed upon by USP and the supplier or this audit may be performed unannounced. For scheduled audits, USP will communicate to the supplier's designated contact person the agenda for the audit, specifying all relevant areas to be covered. The supplier must assure the availability of the required personnel. Whether announced or unannounced, the principles of the *USP-NF* General Chapter <1078 > *Good Manufacturing Practices for Bulk Pharmaceutical Excipients*, and the International Pharmaceutical Excipients Council Pharmaceutical and the Pharmaceutical Quality Group (IPEC/PQG) Good Manufacturing Practices Guide for Pharmaceutical Excipients will be followed. Safety procedures for the areas being audited will be followed.

Auditors will apply the following criteria: (Please See Forms and Checklists, section 14 for the complete list)

Quality Management

- Dedicated quality assurance/quality control department
- Quality manual
- Control of documents and records
- Change control system

Resource Management

- Personnel training
- Personnel hygiene
- Building and facility
- Working environment

Product Realization

- In-process and release specification
- Labeling and delivery requirements
- Selection and approval of the critical suppliers

- Master production and control records
- Complaints and recalls

Measurement, Analysis and Improvement

- Internal audits
- Laboratory controls
- OOS test results
- Retained sample
- Control of impurities
- Stability program
- Assigning expiry and retest period

Control of Non-conforming Product

- Evaluation of nonconforming product
- Disposition of non conforming product

Rejection, Reprocessing and Rework

- Quarantining material not meeting specifications
- Reprocessing, reworking or reusing procedures

Analysis of Data and Improvement

- Product reviews
- Customer complaint and returns
- Internal and customer audits
- Process capability studies

Corrective and Preventive action

- Root cause analysis
- Corrective and preventive action

The on-site audit will be conducted according to the On-Site Audit Checklist (see section 14, 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 supplier along with the Program's report of any actions that the supplier needs to take to correct these deficiencies. The supplier 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 qualification process. For Action Level 1 deficiencies (see section 11, USP Excipient SQP REPORT OF FINDINGS), proof of corrective action, with the date of completion or progress made, must be submitted to USP before the qualification process can continue for the excipient. Follow-up on-site-audit may be necessary before the qualification process can continue. For Action Level 2 deficiencies, the qualification process will

continue, but deficiencies must be addressed and corrective action taken before the qualification letter can be issued for the excipient. For Action Level 3 deficiencies, the excipient manufacturer needs to provide a commitment to address the issues cited with the drug product manufacturer within the specified time period.

11. | USP EXCIPIENT SQP REPORT OF FINDINGS

A report will be issued to the drug product manufacturer listing the final determination and status of any issues regarding the various elements of the USP-Excipient SQP as it pertains to the excipient supplier. The report for each manufacturing site will be segregated according to the following elements of the Program, as applicable:

- Pre-audit Documentation
- On-site Audit
- Analytical Results at all stages of manufacture

The results of the On-Site audit apply to the manufacturing site audited and the excipients manufactured at that site, whereas the testing results 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 of the issue or deficiency. All Action Levels require some action to be taken by the company.

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 major changes to an excipient or process. Action Level 1 issues involve changes to the current quality system. Action Level 1 issues must be adequately resolved before qualification can be given to the excipient supplier, and may require that the supplier's excipient and manufacturing site be resubmitted for qualification.

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 can be resolved by supplying supplemental information or by making minor changes to the excipient or process. Action Level 2 issues do not involve changes to the current quality system. Action Level 2 issues must be adequately resolved before qualification can be given to the excipient supplier.

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 can be resolved by supplying additional information or by making requested changes to the excipient or process. Action Level 3 issues would allow the USP Excipient SQP qualification to be issued

subject to the excipient supplier's commitment to address the issues cited with the drug product manufacturer with in the specified time period.

The status of pre-audit documentation, on-site audit, and analytical testing 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. It is required that a commitment to resolve all the Action level 3 items with the drug product manufacturer with in the specified time period be provided by the excipient supplier prior to USP Excipient SQP awarding qualified excipient supplier status.

FAIL indicates that one or more Action Level 1 or Action Level 2 issues or deficiencies need to be resolved. The excipient supplier would need to make the appropriate change(s) to the excipient or process and most likely may require that the supplier's excipient and the manufacturing site be resubmitted for qualification.

Any major, moderate and minor change, or any other criteria deemed by the excipient supplier to be essential or significant, should be immediately reported in writing to the drug product manufacturer who sponsored the qualification.

After USP Excipient SQP has given qualification status to an excipient supplier, any major, moderate and minor changes to an excipient's specification, process control data, raw material source, equipment, manufacturing site change, testing, or any other essential or significant criteria invalidates the supplier qualification status, until such time that the changes can be evaluated by USP at the request of the drug product manufacturer.

Disclaimer

The excipient supplier understands that compliance with USP Excipient SQP does not constitute compliance with U.S. federal, state, local, or foreign country requirements. The excipient supplier agrees that any sampling, inspections, or tests conducted by USP Excipient SQP are designed only to verify compliance with USP Excipient SQP requirements and do not relieve the excipient supplier of its responsibility to ensure the quality of its excipients in the marketplace or to comply with applicable federal, state, local, or foreign country regulations. Compliance with USP Excipient SQP may not be used as a defense when compliance with legal requirements is an issue. The excipient supplier agrees that USP will not be called to testify or otherwise appear on its

behalf in any regulatory or other legal proceeding brought by a regulatory agency. USP is not an agent of the excipient supplier or acting in capacity thereof.

12. | ISSUANCE AND USE OF THE QUALIFICATION STATUS

On satisfactory completion of the:

- Evaluation of pre-audit documentation
- Evaluation of on-site audit report
- Testing of excipient samples

Formal notification of supplier qualification status will be made by USP Excipient SQP to the drug product manufacturer in writing. The notification will specify which of the excipient supplier's excipient(s) are included in the qualification of the manufacturing site and other limiting information as appropriate. The qualification status is only applicable to excipients supplied from the manufacturing site to the drug product manufacturer who engaged the Program in regard to a particular excipient supplier. The qualification status is not applicable to excipients sold by the excipient supplier to other drug product manufacturers.

Participants and excipient suppliers are reminded, however, that the terms and conditions set forth in the USP Excipient SQP Agreement have precedence over this manual.

13. GLOSSARY

802 Country: a country that is recognized under section 802(b)(1)(A) of the Federal Food, Drug, and Cosmetic Act and to which a drug or device may be exported without having the drug or device approved by the U.S. Food and Drug Administration, if the drug or device complies with the laws of that country and has valid marketing authorization by the appropriate authority. 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., 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.

Agreement: an agreement between USP and the drug product manufacturer who enters into agreement with USP seeking the services of USP to qualify their excipient supplier.

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.

Commercial Scale: The manufacturing of an excipient on production manufacturing scale for commercial use.

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 elected chairs of Expert Committees.

Critical/Key Intermediate: An intermediate in which an essential molecular characteristic(s), usually involving the proper stereochemical configuration required for structure/activity (pharmacological and/or physiological activity of the excipient) is first introduced into the structure (e.g., introduction of a chiral center)

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

EC: USP Expert Committee. One of USP's scientific standard-setting bodies.

EP: *European Pharmacopoeia*.

EPA: U.S. Environmental Protection Agency.

Excipient Deficiencies (Action Level 1): include the following (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) a company official has submitted fraudulent documents to the USP Excipient SQP; or (4) an official organization, such as the FDA, has recommended a voluntary recall.

Excipient Deficiencies (Action Level 2): include the following (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 company, affiliates, or agents engage in violation of any USP Excipient SQP 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.

FDA: U.S. Food and Drug Administration.

Federal FD and C Act: Federal Food, Drug, and Cosmetic Act.

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.

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 an excipient to assure that such excipient meets the requirements as to safety and has the identity and strength, and meets the quality and purity characteristics that it purports or is represented to possess. GMPs are that part of quality assurance which 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, and their acceptance criteria, present in an excipient.

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.

JP: Japanese Pharmacopoeia.

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.

Participant: a company that has qualified to participate in the USP Excipient SQP.

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.

QA: Quality assurance.

QC: Quality control.

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 excipient.

Recall: A supplier's removal or correction of its marketed excipient that the USP Excipient SQP, an official organization such as the FDA, or the company initiates due to a critical excipient deficiency.

Residual Solvents: Organic volatile chemicals that are used or produced in the manufacture of 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: Includes the tests, analytical test procedures, and acceptance criteria that define the standard of quality for a material.

SOP: Standard operating procedure.

Stability Protocol: Documents describing the sample, test specifications, test intervals, conditions, and packaging used to determine the shelf-life.

USP-NF: The current official volume of the *United States Pharmacopeia–National Formulary*, including its supplements.

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.

14. FORMS AND CHECKLISTS

- Pre-Audit Documentation Checklist
- On-Site Audit Checklist

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Excipient Pre-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:			
Pre-Audit Documentation						
Complete documentation, in the requested format, needs to be received before the review may begin.						
Please include Standard Operating Procedures (SOPs) or descriptions of the following in the pre-audit documentation package.			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

USP Excipient 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

GMP ITEM	ACCEPTABLE (A)	NOT ACCEPTABLE (NAc)	NOT APPLICABLE (NAp)	NOT REVIEWED (NR)	COMMENTS OR (C/A) ATTACHMENTS (√= YES)
EXCIPIENT GMP ON-SITE AUDIT CHECKLIST					
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?					
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?					

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GMP ITEM	A	NAC	NAP	NR	C/A
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?					
5.5 Responsibility, Authority, and Communication					
5.5.1 Responsibility and Authority					

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GMP ITEM	A	NAC	NAP	NR	C/A
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 procedures regarding the building and facilities operation?					

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GMP ITEM	A	NAC	NAP	NR	C/A
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?					
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
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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?					

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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)?					
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	NAc	NAP	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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GMP ITEM	A	NAC	NAP	NR	C/A
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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GMP ITEM	A	NAC	NAP	NR	C/A
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 labelled 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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GMP ITEM	A	NAC	NAP	NR	C/A
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?					

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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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GMP ITEM	A	N/Ac	N/Ap	NR
8.2.4.8 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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GMP ITEM	A	NAC	NAP	NR	C/A
8.3.3 Returned Excipients					
8.3.3.1 Are returned excipients identified and quarantined until the quality unit has completed an evaluation of their quality?					
8.3.3.2 Are there a procedures for the holding, testing, reprocessing, or reworking of returned excipients?					
8.3.3.3 Are returned excipients identified and quarantined until the quality unit has completed an evaluation of their quality?					
8.3.3.4 Are records for returned excipients maintained that include the name of the excipient and batch number, reason for the return, quantity returned, and ultimate disposition of the returned excipient?					
8.4 Analysis of Data					
8.4.1 Has the excipient manufacturer developed methods for evaluating the effectiveness of its quality management system and use those data to identify opportunities for improvement?					
8.4.2 Are data derived from customer complaints, product reviews, process capability studies, internal and customer audits analyzed as part of the management review (see also 5.6)?					
8.4.3 Is a periodic review of key indicators such as product quality attributes, customer complaints and product nonconformities conducted to assess the need for improvements?					
8.5 Improvement					
8.5.1 Continual Improvement					
8.5.1.1 Does the excipient manufacturer take proactive measures to continuously improve manufacturing and quality management system processes?					
8.5.1.2 To identify opportunities for continual improvement, does the manufacturer consider the following performance indicators as part of its analysis:					
8.5.1.2.1 Causes of nonconforming product?					
8.5.1.2.2 Results of internal and external audits?					
8.5.1.2.3 Customer returns and complaints?					
8.5.1.2.4 Process and operational failures?					
8.5.2 Corrective Action					
8.5.2.1 Has the excipient manufacturer established, documented and maintained procedures for:					
8.5.2.1.1 Determining the root causes of nonconformities?					
8.5.2.1.2 Ensuring that corrective actions are implemented and effective?					
8.5.2.1.3 Implementing and recording changes in procedures resulting from corrective action?					
8.5.3 Preventive Action					
8.5.3.1 Has the excipient manufacturer established, documented and maintained procedures for:					
8.5.3.1.1 Initiating preventive actions to deal with problems at a level corresponding to the risks?					
8.5.3.1.2 Implementing and recording changes in procedures resulting from preventive action?					
Reported By: _____					
	Printed Name		Signature		Date
Reviewed By: _____					
	Printed Name		Signature		Date

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