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⟨1078⟩ GOOD MANUFACTURING PRACTICES FOR BULK PHARMACEUTICAL EXCIPIENTS

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▲1. INTRODUCTION

This general information chapter provides guidelines for methods, facilities, and manufacturing controls recommended for use in the production of pharmaceutical excipients in order to ensure that excipients possess the quality, purity (i.e., consistent composition), safety, and suitability for the use that they purport to possess. The principles and information in this chapter can be applied to the manufacture of all pharmaceutical excipients [referred to throughout this document as excipient(s)] intended for use in human and veterinary drug products, including biologic drug products. This chapter covers the quality management system (QMS) and the extent of good manufacturing practices (GMPs) necessary throughout manufacturing for both batch and continuous processes.

This chapter combines the concepts of existing GMPs from the following sources:

- International Pharmaceutical Excipients Council (IPEC) & The Pharmaceutical Quality Group (PQG), The Joint Good Manufacturing Practices Guide for Pharmaceutical Excipients (2017)
- EXCiPACT: Certification Standards for Pharmaceutical Excipient Suppliers: Good Manufacturing Practices, Good Distribution Practices. Requirements for Auditor Competency and Third-Party Organizations Providing Certification of the Management System (2021)
- NSF/IPEC/ANSI 363-2019, Good Manufacturing Practices (GMP) for Pharmaceutical Excipients

In view of the increasing globalization of the pharmaceutical industry and the harmonization of pharmaceutical registration requirements, this chapter presents the combination of the most relevant concepts and quality guidelines and standards from industry subject matter experts and the requirements of regulatory agencies around the world. Section *2. General Guidance* provides an overview of the appropriate manufacturing practice criteria applicable to excipient manufacture and the points of application from which to apply excipient GMP and QMS principles. The section also recommends measures that limit contamination of an excipient. No attempt has been made to include details specific to particular excipients. The information in the *Appendix: Auditing Considerations* sets forth key criteria to aid in the audit of an excipient manufacturing facility. For a list of terms used in this chapter and their definitions, see the *Glossary.*

1.1 Purpose and Scope

This chapter defines the point of application and extent of appropriate GMP and QMS principles for excipient manufacture. It is intended to aid both auditors and manufacturers in establishing whether the facilities, equipment, and controls used for the manufacture of excipients are adequate. GMP conformance should help ensure consistent excipient composition. Detailed information pertaining to the excipient manufacturer's intended use (hereafter referred to as "intended use") of an excipient as marketed by the excipient manufacturer and application of risk management principles, can be useful in implementing GMPs. Monographs or appropriate specifications assure that the quality of the excipient is acceptable for use in a drug product. If the appropriate quality standards are not implemented and followed, excipients may pose a hazard to patient safety. Thus, the requirement to have a robust QMS in place that assures the quality of excipients remains imperative, particularly as adulteration of pharmaceutical excipient purity has resulted in many human tragedies.

Some principles in this information chapter may not be applicable to the manufacture of certain excipients because of the diversity of excipients and manufacturing processes. Where appropriate, application, and/or non-application, of the principles in this chapter should be justified in a documented risk assessment.

The manufacture of certain excipients for special applications presents additional challenges that are outside the scope of this chapter. Examples include excipients:

- For parenteral, ocular, inhalation, and open wound use
- Those that are purported to be sterile or pyrogen-free

This chapter does not provide information for all national legal requirements, nor does it cover in detail the particular characteristics of every excipient.

Good distribution practices (GDP) including packaging from bulk, repackaging, and relabeling are covered in *Good Distribution Practices for Bulk Pharmaceutical Excipients* ⟨1197⟩.

1.2 Risk-Based Principles

Raw materials and the processes used to manufacture excipients are very diverse. The use of risk assessments under a quality risk management (QRM) program by the excipient manufacturer will identify those aspects of the raw materials and manufacturing process that require the implementation of GMP controls to minimize the risks to excipient quality and patient safety while maintaining regulatory compliance. Therefore, the excipient manufacturer should undertake and document risk assessments, action plans, and mitigations. These risk assessments, and the resulting mitigations identified, form a key part of the QMS and its documentation. There are many suitable risk assessment approaches and tools that the manufacturer may utilize as suited to their circumstances. The methodologies detailed in The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Q9—Quality Risk Management are applicable to pharmaceutical manufacture.

1.3 Principles Adopted

Materials used as pharmaceutical excipients often have uses other than pharmaceutical applications. Each manufacturer should consider how this general chapter might apply to its products and processes (e.g., batch versus continuous processes, chemical synthesis, extraction, and purification of natural substances, etc.).

2. GENERAL GUIDANCE

2.1 Pharmaceutical Excipients

Pharmaceutical excipients are substances other than the active pharmaceutical ingredient (API) that have been appropriately evaluated for safety and are intentionally included in a drug delivery system. For example, excipients are added to drug formulations to:

- Aid in the processing of the drug delivery system during its manufacture
- Protect, support, or enhance stability, bioavailability, or patient acceptability
- Assist in product identification
- Enhance any other attribute of the overall safety, stability, effectiveness, or delivery of the drug during storage or use

A more complete classification of excipients according to their functions can be found in the *USP and NF Excipients, Listed by Functional Category* section of the *USP–NF*.

2.2 Excipient GMP Implementation

The excipient manufacturer should identify the starting point in the manufacturing process for where the GMP expectations of this chapter apply (full GMP) and document their rationale. Where the process is used to produce materials for different markets, consider whether the batch of product produced is to be sold as a pharmaceutical excipient. If so, determine where in the process the significant structural fragment of the excipient is formed. This may be the earliest point at which full compliance with the expectations of this general chapter might apply. For a synthetic process, this can be the point at which excipient raw material is added to the process to produce the excipient structural fragment. However, based on process knowledge and risk assessment, later points in the process may be justified, i.e., final purification. For other processes such as modification of natural substances, purification of natural substances, and continuous processing, this may be at purification of the significant structural fragment or purification of the final excipient. The application of the principles of excipient GMP apply from an established starting point for GMPs but certain principles may apply earlier in processing, such as a raw material supplier approval, approval of incoming raw materials, etc. The emphasis of GMPs for excipients is to ensure product integrity, avoid product contamination, and ensure that proper records are maintained.

As the excipient manufacturing process progresses, the degree of assurance concerning the quality of the product should increase. Manufacturing processes should be controlled and documented throughout the entire process. However, at some logical processing step, as determined by the manufacturer, the GMPs as described in this chapter should be applied and maintained.

Justification based on a documented risk assessment and a thorough knowledge of the process is required to determine from which processing step GMPs should be implemented. This is often before the final finishing operation and may be identified using methods such as hazard analysis and critical control point (HACCP), failure mode and effects analysis (FMEA), or assessment of a detailed process flow diagram. Consideration should also be given to other factors such as batch versus continuous processing, dedicated versus multipurpose equipment, and open versus closed processes.

3. EXCIPIENT QUALITY MANAGEMENT SYSTEM

3.1 Understanding the Organization and Its Context

The organization should ensure its QMS is suitable for the purpose of supplying excipients. Internal and external factors that are relevant to the quality of the excipient for the intended market should be determined and monitored. Internal and external factors should include the impact of other products produced in the same equipment and outsourced activities (see *6.4 Production and Service Provisions*), for which the organization has control and responsibility that can affect excipient quality. Control measures should be defined. The organization should document and communicate the use for which the excipient is being marketed.

3.2 Understanding the Needs and Expectations of Interested Parties

The organization should determine:

- The interested parties that are relevant to the QMS
- The requirements and expectations of these interested parties

3.3 General Requirements

The principles outlined in this chapter provide a comprehensive basis for the QMS used in the manufacture of pharmaceutical excipients. Excipient manufacturers should implement the quality management processes required to ensure excipient quality. The elements of the quality management processes should be applied in a manner that is appropriate and proportionate to the product life cycle stages, from the starting point of GMP, recognizing the different goals and knowledge available at each stage.

3.4 Determining the Scope of the QMS

The organization should define and document the scope of application of the QMS to its operations and activities. In determining the scope, the organization should consider the internal and external factors and the requirements and expectations of the interested parties (see *3.2 Understanding the Needs and Expectations of Interested Parties*) as well as the quality required for the excipient(s). The organization should determine the appropriate starting point in the manufacture of the excipient where all applicable requirements of this standard apply. Where a clause is not applicable, the organization should document the reason. Conformity to this chapter can only be claimed if the requirements designated as not applicable do not impact the performance of the QMS or adversely impact the quality of the excipient.

3.5 QMS and Its Process

The organization should document, manage, and implement the QMS and GMP required to assure excipient quality and continually improve the QMS and GMP in accordance with this chapter.

In defining the quality management processes, based on risk management, the organization should:

- Define individual and collective roles, responsibilities, authorities, and interrelationships of all organizational units involved with the excipient QMS and ensure these interactions are communicated and understood at all relevant levels of the organization
- Define the interactions of the processes stated herein, with the operations needed for the QMS and the implementation of GMP
- Determine the criteria and methods to ensure that the operation and control of these processes and GMP are effective
- Ensure that there are suitable resources, including availability of information, to support the operation and measurement of these processes
- Monitor, and where applicable, measure and analyze these processes and procedures to gain knowledge and understanding of them

Note that processes here include the QMS, manufacturing, and delivery operations. Apply actions based on science and knowledge gained to improve these processes and the QMS while maintaining consistent excipient quality. QRM may be useful for identifying and prioritizing areas for continual improvement.

3.6 Documentation Requirements

3.6.1 GENERAL

The excipient manufacturer should have a system in place to control documents and data that relate to the requirements of the QMS. The design, organization, and documentation of the quality system should be structured to facilitate common understanding and consistent application throughout the organization.

The use of appropriate QRM principles should be used to assess changes to the QMS. Note that QRM may be a useful aid to identifying activities, operations, and processes that pose a risk to consistent physical, chemical, and/or microbiological excipient quality.

The following documents should be included in the QMS:

- Quality objectives
- Documents and records required by this chapter and any other documents necessary for the effective planning, operation, and control of the processes
- A documented risk assessment that defines and justifies when the applicable clauses in this chapter are not implemented

Note that a single document may address the requirements of one or more procedures and multiple documents may be used to meet the requirement for a documented procedure. Documentation may be in any form or type suitable for long-term storage and retrieval and must be readable.

Note that a Quality Manual is a useful aid to both auditees as well as auditors. The manual facilitates the identification of objective evidence that supports conformance to a clause. The manual also facilitates auditor preparation and efficiency. The manual may contain:

- Description of the QMS and its processes
- Management responsibilities
- The scope of application (including the point in the manufacturing process at which all of the requirements of this chapter are applied)
- The quality policy
- Reference to supporting procedures or a description as to how the requirements of each clause was met
- A commitment of the organization to apply the GMP and QMS requirements contained in this chapter
- Justification why the provisions of a clause do not apply

3.6.2 CREATING AND UPDATING

Documents required by this chapter and those determined by the organization as necessary to implement GMP and the QMS should be controlled. Records are a special type of document and should be controlled according to the requirements specified in *3.6.3 Control of*

Documented Information.

A documented procedure should be established to define the controls needed to:

- Approve documents for adequacy by designated personnel prior to issue
- Periodically review, update as necessary, and reapprove documents
- Ensure that changes and the current revision status of documents are identified
- Ensure that current versions of applicable documents are available at points of use
- Ensure that documents remain legible and readily identifiable
- Ensure that documents of external origin are identified, version controlled, and their distribution controlled
- Prevent the unintended use of obsolete documents and to apply suitable identification to them if they are retained for any purpose

Procedures that impact excipient quality should have a defined owner and be reviewed and approved by the quality unit including changes to these documents (see *4.4 Responsibility, Authority, and Communication*). Electronic documentation should meet the requirements for the document control system stated above. If electronic signatures are used on documents, they should be controlled to provide equivalent security to that given by a handwritten signature. Note that electronic documents and signatures may also need to satisfy local regulatory requirements.

3.6.3 CONTROL OF DOCUMENTED INFORMATION

Records should be established and maintained to demonstrate achievement of the defined specifications and conformance with this chapter. Records should be legible and stored in such a manner that they are readily retrievable. Electronic records should be subjected to the same stringency of controls as those required for other records and conform with local regulations, if applicable. All records, electronic and paper, should follow the principles of ALCOA (attributable, legible, contemporaneous, original, and accurate). Pertinent subcontractor quality data should meet the provisions of this section.

Measures should be taken to maintain data integrity. The inherent risks to data integrity may differ but data systems should be configured to avoid any risk of potential manipulation.

Entries in records should be clear, permanent, made directly after performing the activity (in the order performed), signed or attributed to an individual (for electronic records), and dated by the person making the entry. Corrections to entries should be signed and dated, leaving the original entry legible.

Records should be maintained to demonstrate achievement of the required quality and the effective operation of the QMS. Records should be legible and identifiable to the product and lot(s) involved. The organization should define which records, results, and reports of subcontractor activities are retained and by whom.

The record retention period should not be less than one year past the excipient's expiry or two years past the retest date. If the manufacturer does not stipulate an expiry or retest/reevaluation interval, the record retention period should be a minimum of five years from the date of manufacture. Documented procedures should be implemented to ensure control of certificates of analysis (COAs). Different periods of retention time are acceptable when risk assessment is carried out and justified as needed. Records should be stored and maintained in such a manner that they are readily retrievable, in facilities that provide an environment suitable for minimizing deterioration or damage. Procedures should be periodically reviewed, updated as necessary, and reapproved. Measures should ensure that obsolete documents are not used.

3.6.4 CHANGE MANAGEMENT

There should be a documented procedure, where, based on risk management, the manufacturer should evaluate and approve changes that may impact the quality of the excipient, including the impact on any regulatory submissions by the excipient manufacturer. The organization should define the criteria for a significant change. There should be a written procedure, based on risk management, for determining which changes to communicate to customers, as well as a mechanism for communicating such changes. Significant changes should be communicated with sufficient notice prior to implementation as is reasonably practical to customers (see *6.2.1 Determination of Requirements Related to the Product*) and, as applicable, to regulatory authorities. The customer should be informed prior to the first shipment of the excipient after the change is implemented. Documentation generated for change control should be retained (see *3.6.3 Control of Documented Information*).

Changes to the QMS should be performed in a structured manner with consideration for, as appropriate:

- Implementation of intended changes
- Changes to roles and responsibilities
- Impact of the two previous points on interested parties
- Risks and opportunities arising from the changes have been evaluated
- Impact on objectives and the plan to realize them
- Discontinuation of manufacture of an excipient

If it has been determined that a change impacts an interested party (internal and/or external), then that party shall be notified. The evaluation and approval of planned changes should occur prior to the implementation of the changes. Upon implementation, the effectiveness of a change should be confirmed. The quality unit should approve any changes that, based on risk assessment, may impact the quality of the excipient.

Risk assessment (see *1.2 Risk-Based Principles*) should be used to evaluate the potential impact of proposed changes on product quality. The level of formality of the evaluation should be commensurate with the level of risk to product quality.

4. LEADERSHIP

4.1 Management Commitment

Top management should demonstrate to the organization the importance they place on customer satisfaction and compliance with the appropriate regulations and standards. This is demonstrated through provision of resources, assigned roles, responsibilities, and authorities; monitoring conformance to this chapter; and a timely and effective communication and escalation process. This should be accomplished through the development of a quality policy and establishment of quality and GMP objectives. Progress toward the documented quality objectives should be reviewed continuously, or continually (at a minimum, annually).

Top management should have the responsibility to:

- Ensure an effective excipient QMS is in place to achieve the quality and GMP objectives
- Ensure that roles, responsibilities, and authorities are defined, communicated, and implemented
- Ensure the availability of resources
- Communicate to the organization the importance of conforming to the quality policy and support achievement of the quality objectives
- Provide evidence of its commitment to meeting and monitoring ongoing conformance to the requirements of this chapter, the relevant statutory and regulatory requirements, and customer expectations
- Ensure a timely and effective communication and escalation process to top management exists to raise issues of conformance to this chapter that may impact the quality of the finished excipients or changes to regulatory requirements
- Ensure management reviews are conducted on a regular basis
- Ensure customer key requirements are identified, established, and met

Note that top management have overall responsibility for the QMS. However, some tasks may be delegated to others.

Note that customer key requirements as they relate to this chapter include suitable facilities, competent and trained personnel, and operations designed to promote excipient integrity, avoidance of cross-contamination, consistent excipient composition, and the ability to produce excipient conforming to the customer specifications.

4.2 Quality Policy

Top management should demonstrate its commitment to the corporate quality policy and ensure that it is implemented within the operational unit. Top management should commit to participate in the development of the company's quality policy and provide the resources necessary for its development, maintenance, and deployment.

The quality policy should:

- Include commitments to implementation of the appropriate GMP, compliance with applicable regulatory requirements, and continual improvement
- Be communicated to and understood by personnel at all levels in the organization
- Be periodically reviewed

As part of the quality policy, the excipient manufacturer should allow the customer to evaluate the effectiveness of their QMS, manufacturing processes, buildings, and facilities, etc. Otherwise, the excipient manufacturer should provide other means for the customer to assure the site conforms to the requirements of this chapter such as third-party audit or certification.

4.3 Planning

4.3.1 ACTIONS TO ADDRESS RISK AND OPPORTUNITIES

The organization should use the internal and external factors identified in the section *3.3 General Requirements* and expectations of the interested parties to develop a QMS that provides assurance that the excipient(s) meet the expectations of the interested parties and regulatory requirements.

Note that regulatory requirements are the minimum quality standard. Customer requirements are an add-on that cannot conflict with the regulatory requirements.

The organization should identify and document the risks that could impact the effectiveness of the QMS and the quality of the excipient. These risks should be regularly reviewed and actions taken in proportion to their potential impact on the QMS, the quality of the excipient, and/or the expectations of the interested parties. The effectiveness of the actions should be reviewed during management review (see *4.5 Management Review*). Improvement to the QMS and reduction of risks to excipient quality should also be considered and implemented where appropriate (see *7.5.1 Continuous Improvement*).

Note that risks to excipient quality can affect the excipient itself (e.g., contamination) or be the result of defects in the QMS (e.g., inability to trace a batch).

4.3.2 QUALITY OBJECTIVES AND PLANNING TO ACHIEVE THEM

Top management should ensure quality objectives are established for relevant functions and levels within the organization for adherence to the appropriate GMP. The organization should maintain, regularly review, and document its performance against those quality objectives. Quality objectives should be deployed throughout the organization and should be understood, measurable, and consistent with the quality policy.

4.3.2.1 Planning of changes: Changes to the QMS should be performed in a structured manner, consistent with section *3.6.4 Change Management*.

4.3.3 QUALITY MANAGEMENT SYSTEM PLANNING

Top management should provide adequate resources to ensure conformity to the provisions of this chapter. There should be a process for the identification of resources needed for adherence to GMP. A gap analysis based on audits by internal personnel, customers, regulatory agencies, or outside contractors, or based on the use of this chapter, could provide the basis to identify resource requirements. Top management should ensure that the integrity of the QMS is maintained when changes are planned and implemented.

4.4 Responsibility, Authority, and Communication

4.4.1 RESPONSIBILITY AND AUTHORITY

Responsibility and authority should be clearly defined by top management and communicated within the organization. It should be the responsibility of a unit that is independent of production, such as the quality unit, to do the following:

- Ensure that quality-critical activities are undertaken as defined
- Approve suppliers of quality-critical materials and services
- Approve or reject raw materials, packaging components, intermediates, and finished excipients, according to current approved specification
- Ensure that there is a review of production records to confirm that no errors have occurred or, if errors have occurred, that they are fully investigated, corrected, prevented from reoccurring, and properly documented, including any corrective or preventive actions
- Participate in reviewing and authorizing changes that potentially affect quality such as to processes, specifications, procedures, and test methods prior to implementation (see *6.2.5 Changes to Requirements for Products and Services* and *3.6.3 Control of Documented Information)* and participate also in investigating failures and complaints
- Retain responsibility for approval or rejection of the excipient if it is produced, processed, packaged, or held under contract by another company
- Develop and implement a self-inspection program of the QMS
- Ensure that outsourced service providers have agreed to comply with relevant sections of this chapter

The quality unit may delegate some of its activities to other personnel if appropriate controls (e.g., periodic audits, training, and documentation) are in place.

An organization chart by function should show interdepartmental relationships as well as relationships to top management of the company. Personnel whose positions affect excipient quality should have job descriptions.

4.4.2 INTERNAL COMMUNICATION

Top management should ensure that appropriate systems are established to communicate GMP and regulatory requirements, quality policies, quality objectives, and procedures throughout the organization. The communication should also provide information about the effectiveness of the QMS. Based on risk assessment, top management should be notified promptly of quality-critical situations, such as product retrievals (i.e., recalls), in accordance with a documented procedure.

4.5 Management Review

4.5.1 GENERAL

Top management of the company should hold regular (at least annual) reviews of the QMS to confirm the organization's continued conformity to this chapter. The review should be recorded and should include assessing opportunities for improvement and the need for changes to the QMS. Such changes should be assessed and implemented via the change control procedure (see *3.6.3 Control of Documented Information*).

4.5.2 REVIEW INPUT

Management review inputs should include the following:

- 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
- New, revised, and proposed compendial and regulatory requirements
- Changes that could affect the QMS

4.5.3 REVIEW OUTPUT

The management review should identify the resources needed and the opportunities presented for improving the QMS and improving product conformity to customer and regulatory requirements. A record should be made of actions recommended and taken and their completion.

5. SUPPORT

5.1 Resources

The organization should identify the need and provide the required qualified personnel and resources (e.g., equipment, materials, buildings, and facilities) to implement, maintain and improve the QMS and to produce, package, test, store, and release each excipient in a manner consistent with this chapter.

Note that a gap analysis based on audits or other means of evaluation by internal personnel, customers, regulatory agencies, or outside contractors and based on this chapter may be used for the purpose of identifying resource requirements.

5.2 People

5.2.1 GENERAL

Personnel who have a direct or significant impact on excipient quality should have job descriptions and defined responsibility and authority. Personnel performing and supervising work with the potential to affect the quality of excipients should have the appropriate combination of education, training, and experience to perform their assigned tasks.

Consultants advising on the design, production, packaging, testing, or storage of excipients should have the education, training, and experience or any combination thereof that qualifies them to advise on the subject for which they are retained. The organization should maintain records listing the name, address, and qualifications of consultants and the type of service they provide.

5.2.2 COMPETENCE, AWARENESS, AND TRAINING

The excipient manufacturer should establish and maintain procedures for identifying training needs and for providing the necessary training to personnel performing activities affecting excipient quality (including external and contract personnel), prior to performing those activities. Appropriate records of training should be maintained. Training should address the particular operations that the employee performs and applicable GMP requirements as they relate to the employee's responsibilities.

Continuous training based on risk management should be planned. Qualified individuals should conduct GMP training to ensure that employees remain familiar with applicable GMP principles. Management should establish adequate and continued personal hygiene training for personnel who handle materials so that they understand the precautions necessary for preventing contamination of excipients. The training program should ensure that personnel understand that deviations from procedures may affect the pharmaceutical customer's product quality and patient safety.

5.2.3 PERSONNEL HYGIENE

To protect excipients from contamination, the organization should conduct a documented risk assessment to identify areas where the excipient is at risk of contamination from personnel or their activities. The following should be considered at a minimum to protect the excipient from contamination:

- Use of protective apparel such as head, face, hand, and arm coverings should be worn as appropriate to the duties performed
- Jewelry and other loose items, including those in pockets, should be removed or covered in order to avoid the opportunity for loose items to fall into the excipient
- Only authorized personnel should enter the areas of the buildings and facilities designated as limited-access areas

Personnel should practice good sanitation and health habits. Any person shown by either medical examination or supervisory observation to have an apparent illness or open lesions that may adversely affect the safety or quality of the excipient should be excluded from direct contact with raw materials, packaging components, intermediates, and finished excipients until the condition is corrected or until competent personnel determine that it will not jeopardize the safety or quality of the excipient.

- Personnel should be instructed to report to supervisory personnel any health conditions that may have an adverse effect on excipients.
- The storage and use of food, drink, personal medication, tobacco products, or similar items should be restricted to designated locations where the excipient is not exposed to risk of contamination.
- Movement of personnel between areas used in the manufacture or control of highly sensitizing or toxic materials and excipient manufacturing areas is strongly discouraged. If it is required, full decontamination procedures should be followed.

Suitable control measures should be implemented to mitigate the identified risks.

5.3 Infrastructure

Infrastructure should be managed, operated, cleaned, and maintained in accordance with GMP principles to ensure excipient quality and to avoid contamination (including, where appropriate, control of particulate matter, microbiological organisms, and water quality).

5.3.1 BUILDINGS AND FACILITIES

Contamination prevention should be considered in the design, maintenance, refurbishing, or upgrading of buildings and facilities.

The organization should conduct a risk assessment based on the intended use of the excipient to identify areas in which the excipient is at risk of contamination, cross-contamination, or mix ups due to deficiencies in buildings and/or facilities. The risk assessment should consider the following, at a minimum, to identify where the excipient is at risk of contamination:

- State of repair of the building and facility
- Suitability of size, construction, and location

- Ability to maintain a suitably clean building and facility environment
- Operations inside or outside of the building or facility that may affect the excipient quality
- Presence of environmental contaminants, including microorganisms

Suitable control measures should be implemented to mitigate the identified risks. Access to areas of the buildings and facilities designated as limited access areas should be controlled.

Manufacturing processes associated with the production of highly sensitizing (e.g., allergens) or toxic products (e.g., herbicides and pesticides) should be located in dedicated facilities or should use equipment separate from that used for excipient manufacture. If this is not possible, appropriate measures (e.g., cleaning or inactivation) should be implemented to avoid cross-contamination. The effectiveness of these measures should be demonstrated. There should be adequate facilities for the testing of raw materials, packaging components, intermediates, and finished excipients.

5.3.2 EQUIPMENT

Equipment used in the production, processing, packaging, testing, or storage of an excipient should be:

- Maintained in a good state of repair and should be of suitable size, construction, and location to facilitate cleaning, maintenance, and correct operation. The nature of the cleaning, maintenance, and correct operation may vary depending on the type of processing equipment (e.g., batch versus continuous). A risk management process should be performed to define activities and suitable controls such as commissioning and qualification according to the intended use, to ensure the correct equipment operation and quality of the excipient.
- Change parts, utensils, and hoses should be cleaned and stored to maintain their fitness for use
- Where equipment is located outdoors, there should be suitable controls to minimize the risk to excipient quality from the environment (e.g., processing within a closed system).
- Constructed so contact surfaces will not be reactive, additive, or absorptive
- Designed, installed and stored when disconnected so as to assure proper sanitary condition, including appropriate provisions for drainage

Design deficiencies that may impact excipient quality should be addressed as part of routine risk management by a risk assessment exercise that includes as an output a mitigation strategy for the deficiencies noted in the risk assessment.

5.3.3 EQUIPMENT DESIGN AND CONSTRUCTION

New installations or replacement equipment should be designed and constructed to minimize the possibility of contamination and should be demonstrated before use to be functioning as intended.

In the design and construction of equipment, the risk of contamination from process materials or other media used for proper equipment operation (e.g., lubricants and heat transfer fluids) coming into contact with raw materials, packaging components, intermediates, or finished excipients should be identified. When risks are identified, they should be mitigated to minimize the possibility of contact with the process stream and documented. Where contact is possible, materials suitable for food contact should be used unless otherwise justified.

To control the risk of contamination, equipment with moving parts should be assessed regarding the integrity of seals and packing materials.

Additionally, ergonomic considerations along with personnel safety should be a part of the user requirements for equipment design and installation.

5.3.4 EQUIPMENT MAINTENANCE

Procedures and associated schedules, unless otherwise justified based on a documented risk assessment, should be established for the maintenance of equipment and calibration of instruments used in the production, processing, packaging, testing, and holding of the excipient. Deviations from the normal maintenance schedule should be justified.

There should be chronological records of the use, maintenance, and associated cleaning of equipment coming into contact with the process stream.

Corrective maintenance should be documented and justified. If there is any change in the configuration or spare parts from the original, it should be handled under documented change control and evaluated using a documented risk assessment to determine the level of the impact to the qualification status of the equipment and quality of excipient.

Deviations from the normal maintenance schedule should be justified. The sequence of activities with the equipment can be established through a log dedicated to the equipment or a combination of records such as maintenance, calibration, cleaning, and batch records.

5.3.5 COMPUTER SYSTEMS

The organization should identify those computer systems that may impact QMS and those that may impact excipient quality.

Those that may affect excipient quality should have sufficient controls to ensure:

- Consistent operation of the system
- Prevention of unauthorized access or changes to computer software, hardware, or data
- Evidence that equipment or automated systems used in production and control are capable of performing their designated function
- Disaster recovery procedures, including retention of suitable back-up or archival systems
- Maintenance and assurance that changes are verified and documented and only made by authorized personnel
- Provisions to assure the maintenance of data and data integrity in accordance with the principles of ALCOA

- Systems and procedures that show that the equipment and software are performing as intended and at appropriate intervals
- Changes to the system are conducted in accordance with section *6.2.5 Change to Requirements for Products and Services* of this general chapter

Those computer systems that may only impact the QMS should have sufficient controls to ensure:

- Consistent operation of the system
- Prevention of unauthorized access or changes to computer software, hardware, or data
- Disaster recovery procedures, including retention of suitable back-up or archival systems
- Maintenance and assurance that changes are verified and documented and only made by authorized personnel
- Changes to the system are conducted in accordance with section *3.6.4 Change Management* of this general chapter

5.3.6 UTILITIES

The organization should conduct a risk assessment considering the risk to excipient quality from utilities intended to or with the potential to come into contact with the excipient (utilities can include nitrogen, compressed air, steam, and water). Control measures should be implemented to mitigate the identified risks and documented.

Utilities coming into direct contact with the excipient during its manufacture or surfaces that could contact excipients should have documented specifications to assure that the utility is suitable for its intended use.

5.3.7 WATER

Unless otherwise justified, water should, at a minimum, meet the World Health Organization (WHO) Guidelines for Drinking-Water Quality or Environmental Protection Agency (EPA) guidelines for potable water, be distributed in a well designed sanitary system, and be provided either under continuous positive pressure or with other robust means of preventing back flow. Water quality limits should be consistent with the desired excipient intended use. The water purification system and process should be specified, and the quality of the water should be monitored and controlled within appropriate microbiological and chemical limits based on intended use of the excipient. Where there is water available of multiple qualities, provisions should be made to avoid mix ups.

If interruptions to supply or deviations in the quality of such water occur, evidence and appropriate rationale should be documented to show such deviations or interruptions have not compromised the quality of the excipient. Production should not recommence until it has been shown that the water has returned to its designated quality.

5.4 Work Environment

Where the excipient is exposed during manufacture, it should be in an environment appropriate for minimizing contamination.

The organization should conduct a documented risk assessment to identify areas in which the excipient is at risk for contamination from exposure to the work environment and determine the hazards to excipient quality and the necessary controls.

The documented risk assessment should include marketed use (see *1. Introduction*), customer requirements (see *6.2.2 Review of Requirements Related to the Product*), and, as applicable, should consider the following controls:

- Air handling systems
- Controlled environments
- Cleanliness and sanitary conditions
- Waste segregation and disposal
- Pest control
- Other risk assessments required by this chapter

A documented risk assessment should be carried out to determine the necessary controls. Controls should be implemented, monitored, and documented. Where necessary, workers should be provided with personal protection equipment or other controls to mitigate the risk.

5.4.1 AIR HANDLING

Where the risk assessment has identified that an air handling system poses a potential risk to excipient quality, the air handling system should be designed and maintained to assure adequate protection of the excipient. The organization should demonstrate its effectiveness and suitability, including dedicating processing areas to the same excipient, if a portion of the exhaust air is recycled into the same area.

5.4.2 CONTROLLED ENVIRONMENT

Where the risk assessment has identified the need for a controlled environment because of sensitivity of the excipient to contamination or degradation caused by exposure to heat, air, or light, the environmental conditions should be monitored to assure excipient quality is maintained.

Where an inert atmosphere is required, the gas should be treated as a raw material as defined in section *6.3.3 Verification of Purchased Product*.

If interruptions in the controlled environment occur, the organization should perform an investigation to obtain adequate evidence and appropriate rationale to show such interruptions have not compromised the quality of the excipient. Such environmental concerns become increasingly important following purification of the excipient.

5.4.3 CLEANING AND SANITARY CONDITIONS

Adequate cleanliness is an important consideration in the design of excipient manufacturing facilities. Facilities should be maintained in an appropriately clean and sanitary condition according to the type of processing conducted. Where a risk assessment has identified that

clean and/or sanitary conditions of the work environment are necessary to protect excipient quality, the organization should document procedures assigning responsibility for cleaning and/or sanitation. These procedures should be followed, and cleaning and/or sanitation should be documented, and records should be maintained.

5.4.4 WASTE SEGREGATION AND DISPOSAL

Waste should be segregated, labeled as appropriate, and disposed of in a manner appropriate to its type (e.g., chemical, biological, hazardous). Waste should be disposed of in a timely manner. If waste is not disposed of immediately, it should be suitably identified and stored.

5.4.5 PEST CONTROL

Buildings should be free from infestation by rodents, birds, insects, and other vermin.

Risk assessment may be used to determine specific pest control requirements. This assessment may be carried out by a specialist contractor and should comply with local regulations (when applicable). The excipient manufacturer should document the pest control program. The use of suitable rodenticides, insecticides, etc. should be documented. Where a service provider is utilized, there should be a contract in place.

5.4.6 LIGHTING

Adequate lighting should be provided to facilitate cleaning, maintenance, and proper operations.

Where the excipient is exposed to the work environment or stored, lighting should be shatter-proof or otherwise protected.

5.4.7 DRAINAGE

In areas where the excipient is open to the environment or stored, drains should be of adequate size and, where connected directly to a sewer, should be provided with an air break or other mechanical device to prevent back-siphoning.

5.4.8 WASHING AND TOILET FACILITIES

Adequate personal washing facilities should be provided, including hot and cold water, soap or detergent, air dryers or single-service towels, and clean toilet facilities easily accessible to working areas. These facilities should be separate from but accessible to the work environment. Where identified by risk assessment, facilities for showering and/or changing clothes should be provided.

5.4.9 MONITORING AND MEASURING RESOURCES

The organization should use calibrated and/or verified measuring and test devices. Such measuring and test devices should have appropriate specificity and sensitivity. Records of calibration and/or verification results should be maintained.

The organization should establish a list of procedures for the calibration and maintenance of all measuring and test devices, including computerized systems, unless otherwise justified. The control program should include the standardization or calibration of measuring and test devices at suitable intervals. This program should contain specific limits for accuracy and precision, and provisions for remedial action if accuracy and/or precision limits are not met. Calibration and confirmation standards should be traceable to applicable national, international, or compendial standards. Where no such standards exist, the basis used for calibration or verification should be justified and documented.

The calibration status of equipment should be identified and accessible to the user of the equipment.

If a measurement or test device is found out of calibration, a documented investigation should be conducted to determine the validity of results since the last calibration or documented measurement confirmation. Appropriate action should be taken based on the results of the investigation and documented.

5.4.10 ORGANIZATION KNOWLEDGE

The organization should demonstrate that it has the knowledge to meet the needs of the interested parties, manufacture the excipient, and support the QMS. The organization should have knowledge of the laws and regulations concerning the intended use of their excipients as marketed. When changes are applied to the QMS (see *3.6.4 Change Management*) or the excipient (see *6.2.5 Changes to Requirements for Products and Services*) the organization should perform a gap analysis between the current knowledge and what is required. The organization should acquire the new knowledge.

Note that knowledge should be aligned to the claims made about the excipient, its intended uses, and the countries in which it is marketed.

5.4.11 COMMUNICATION

The organization should ensure appropriate systems are established to communicate throughout the organization the requirements of this general chapter and applicable regulatory requirements. The communication should also provide information about the effectiveness of the excipient QMS.

Based on risk assessment, top management should be notified in a timely manner of events that affect excipient quality and should support appropriate corrective and preventive actions, in accordance with a documented procedure.

6. OPERATION

6.1 Operational Planning and Control

The excipient manufacturer should plan and develop the processes and controls needed for product manufacture including implementation of identified actions from risk management described in other sections of this chapter. Key aspects of planning a suitable process and its controls should include the following, as appropriate:

- Documented testing programs, for materials used in the manufacture of excipients, with appropriate specifications, sampling plans, and test and release procedures
- Records that provide evidence that these plans have been realized as intended and that enable traceability to be demonstrated (see *6.5.1 Traceability*)
- Human resources, laboratory equipment, and facilities for storage and testing [including process analytical technology (PAT)] used in the manufacture and supply of the excipient
- Testing programs for the finished excipient that include appropriate specifications, sampling plans, and test and release procedures
- Actions from relevant documented risk management

The record system should demonstrate that these processes and controls were followed.

The use of recycled or recovered materials containing recoverable amounts of excipient, reactants, or intermediates meeting appropriate specifications should be justified.

6.2 Customer-Related Processes

6.2.1 DETERMINATION OF REQUIREMENTS RELATED TO THE PRODUCT

The excipient manufacturer should determine the excipient quality, labeling, and delivery requirements of the customer. Additional requirements, whether legal, or regulatory (e.g., conformance with a compendial monograph and/or general chapter), should be agreed on by both parties (see *6.2.3 Customer Communication*) and documented. Additional requirements may include:

- Compendial general requirements
- Transmissible spongiform encephalopathy and bovine spongiform encephalopathy (TSE/BSE) statement
- Residual solvents statement
- Elemental impurities statement
- Identification of impurities originating from raw materials of natural origin, e.g., mycotoxins, pesticide residues
- Potentially reactive, mutagenic and/or toxic impurities [for example, ethylene glycol (EG), diethylene glycol (DEG), nitrites, peroxides, aldehydes, etc.] statements

6.2.2 REVIEW OF REQUIREMENTS RELATED TO THE PRODUCT

The excipient manufacturer and customer should mutually agree upon the requirements identified in section *6.2.1 Determination of Requirements Related to the Product*, before supply commences. The manufacturer should have the facility and process capability to consistently meet the mutually agreed-upon specifications. Where the requirements determined in section *6.2.1 Determination of Requirements Related to the Product*, are changed, this review should be repeated before supply recommences.

6.2.3 CUSTOMER COMMUNICATION

There should be provision for providing accurate and pertinent communication to the customer. The organization should determine the types of excipient quality-related documents to be shared with customers. The following processes should be in place:

- At a minimum, master copies of quality-related documents made available to customers should be controlled within the organization
- Provision should be made for formally documenting mutually agreed-upon customer requirements and contracts
- Communication of the origin and traceability of the excipient to the customer
- Requirements not stated by the customer but necessary for specified or intended use, where known
- Notification of changes requiring prior approval from the customer, where determined
- Customer notification of issues detected after delivery of the excipient
- Documentation of customer feedback and complaints
- Definition of how potentially significant changes which may impact the excipient are communicated to customers (also see *6.2.5 Changes to Requirements for Products and Services*)

6.2.4 CUSTOMER COMPLAINTS

Written procedures describing the handling of all written and oral customer complaints should be established and followed. Such procedures should include provisions for recordkeeping, timely review and investigation of complaints, communication of findings to the customer, and follow up activities.

6.2.5 CHANGES TO REQUIREMENTS FOR PRODUCTS AND SERVICES

Top management should establish and maintain a robust change control program under the QMS (see *Significant Change for Bulk Pharmaceutical Excipients* ⟨1195⟩). This program should be designed to ensure that excipient quality is assessed and maintained in accord with principles of QRM when changes are planned and implemented, respectively.

6.2.6 DESIGN AND DEVELOPMENT

Full GMPs are not always applicable during the design and development of new excipients and/or manufacturing processes. However, design and development process and manufacture of experimental batches of excipients that are intended for use in drug products should

follow the principles of Quality by Design and be manufactured in accordance with the applicable provisions of this chapter.

When an industrial grade chemical compound is marketed as excipient, quality should be verified by the consistency of components that make up the excipient and a capable process manufacturing the excipient.

When a new excipient is developed, safety of the material should also be verified. Technology transfer and scaling process should be completed prior to full-scale manufacturing.

6.3 Control of Externally Provided Processes, Products, and Contract Services

6.3.1 GENERAL

The organization should establish a documented system for selecting, approving, and reapproving suppliers of materials and services. The organization's Quality Unit should undertake a risk assessment to determine materials and services that have the potential to impact excipient quality and approve such suppliers.

Material supplier approval by the quality unit should require an evaluation of the supplier's QMS, including adequate evidence that they can consistently meet agreed-upon specifications and maintain traceability. There should be a procedure that describes the assessment of suppliers to ensure they meet the expectations of the excipient manufacturer. The procedure should require periodic reassessment to confirm continued supplier conformance. Records of these activities should be maintained.

Materials should be purchased against a mutually agreed-upon specification. For those materials that are identified as quality-critical, excipient manufacturers should have an agreement with the supplier for a change notification. In the absence of such agreement, a risk assessment should be undertaken to demonstrate that a change by the material supplier will not impact excipient quality. The organization should require that contract service providers adhere to the relevant sections of this chapter. Where manufacturing, testing, or other operations that may affect excipient quality are outsourced, the responsibilities for excipient quality and control measures applicable to this chapter should be defined and documented.

6.3.2 PURCHASING INFORMATION

Purchasing agreements should describe the material or service ordered, including, where critical to excipient quality, the following:

- The name, item code number, type, class, style, grade, or other precise identification traceable to the raw material and packaging specifications

6.3.3 VERIFICATION OF PURCHASED PRODUCT

The organization should establish procedures to verify, approve, and release quality critical purchased material used for excipient manufacture and packaging. The organization should justify and document any material not sampled prior to approval and release, such as when the material is too hazardous or toxic to sample and test.

The organization should verify that the measurements reported on the supplier COA for each lot meet the agreed specification. For packaging components, the organization should verify the certificate of conformance references the current agreed specification. Wherever feasible, the organization should perform at least an identification test or otherwise confirm the identity of the material. Procedures should describe the quarantine of purchased materials prior to their approval. Where quarantine of unapproved material is not possible, the organization should have an agreement with the supplier, so they are promptly notified of material that does not meet specifications.

Any sampling activities should be performed in accordance with a defined method for obtaining representative samples and using procedures designed to prevent contamination and cross-contamination. The organization should establish controls to assure materials delivered in bulk or returned and reused containers are free from contamination and fit for its intended purpose. These procedures, activities, and results should be documented.

6.4 Production and Service Provisions

6.4.1 CONTROL OF PRODUCTION AND SERVICE PROVISION

Production activities should be carried out under controlled conditions (also see *6.1 Operational Planning and Control*). Specific examples of important controls, some of which may not be applicable to all excipient manufacturers, are illustrated in the following sections.

6.4.2 PRODUCTION INSTRUCTIONS AND RECORDS

Production instructions and records are required but may differ for the type of operation (e.g., batch versus continuous processes).

There should be a control document that describes how the excipient is produced (e.g., master production instructions, master production and control records, or process definitions).

For batch processes, an accurate reproduction of the appropriate master production instructions should be issued to the production area. For continuous processes, a current processing log should be available.

Production instructions that describe the manufacture of the excipient and that establish records should provide sufficient detail to ensure the following:

- The excipient was manufactured and packaged according to the production instructions
- Documentation to demonstrate activities were performed in conformance with excipient production requirements
- The identification of individuals performing such activities
- The traceability of materials (including recycled and recovered materials)
- The identification and traceability of equipment used, its maintenance, and cleaning

Records should be available for each batch of excipient produced and should include complete information relating to the production and control of each batch. For continuous processes, the batch and its records should be defined (e.g., based on time or defined quantity). Records may be in different locations but should be readily retrievable.

Records for both batch and continuous processing, where critical to excipient quality, should include the following:

- Date and time each step was completed
- A log of key parameters together with conformance check against specified operating ranges
- Identification of persons (e.g., initials traceable to the individual) performing and directly supervising or checking each significant step, operation or control parameter
- Inspection of manufacturing areas before and after use
- Identification of major equipment and lines used
- Material inputs to enable traceability (e.g., batch number and quantities of raw material/intermediate and time it was added)
- In-process and laboratory control results
- A statement of theoretical yield and allowable range (deviations should be investigated):
    - For excipients produced using batch processing, the quantity as a percentage of theoretical yield, unless otherwise justified
    - For excipients produced using continuous processing, yields should be monitored to ensure they fall within the established range
- Inspection of the packaging and labeling area before and after use
- Labeling control records
- Description of excipient product containers and closures
- Description of sampling performed
- Failures, deviations, and their investigations

6.4.3 Results of Final Product Inspection

State of process control is confirmed using documented in-process testing. Packaging and labeling control procedures should ensure that the packaged lot is traceable to the production and packaging records. Provisions should ensure that the containers are not mislabeled as to lot and/or product.

When excipient is repackaged, the original dates of manufacture and expiry or retest period should be retained unless there is scientific justification otherwise.

6.4.4 Equipment Cleaning

Risk assessment may be used by the manufacturer to design and justify cleaning and sanitization procedures. Evidence of their effectiveness should be provided based on predetermined acceptance criteria. In multipurpose plants, the use of the "model product approach" (groups of products of similar type) may be used in justifying a suitable procedure.

Cleaning and sanitization procedures should be documented. Records of cleaning and sanitization should be available to indicate the cleanliness or sanitization status.

Equipment and utensils should be cleaned and sanitized as needed to ensure excipient quality and performed at appropriate intervals to prevent contamination and cross-contamination of the excipient. The rationale of this interval and cleaning status of equipment should be appropriately documented.

Where disinfectants and/or detergents are required for cleaning, an assessment of their suitability should be documented.

Where multipurpose equipment is in use, it is important to be able to determine previous usage when investigating cross-contamination or the possibility of such contamination (also see *6.4.8 Records of Equipment Use*).

During a production campaign, incidental carryover frequently occurs, and it is usually acceptable because cleanup between successive batches of the same excipient may not be required in order to maintain quality levels.

Products that leave residues that cannot be effectively removed should be produced in dedicated equipment.

For continuous processing, the frequency of equipment cleaning should be determined by risk management and justified.

6.4.5 Blending or Mixing

In-process blending or mixing to facilitate processing or to ensure batch uniformity should be controlled and documented. If the intent of the operation is to ensure batch uniformity, it should be performed so as to ensure homogeneous mixing of materials to the extent feasible and should be reproducible from batch to batch.

Other acceptable blending operations for finished excipients include, but are not limited to:

- Blending of small batches to increase batch size
- Blending of isolated excipient left over from excipient packaging from batches of the same excipient to form a single batch

The blending process should be documented and should allow traceability back to the individual batches that make up the blend. There should be documented scientific justification for the shelf life assigned to the blended batch.

Blending processes should be adequately controlled to ensure homogeneity of the combined batch.

The blended batch should be tested for conformance to established specifications. If the final blended batch does not meet specification, it should be handled per *7.2.3 Control of Nonconforming Materials* and *7.2.8 Reworking*.

6.4.6 In-Process Control

In-process inspection, sampling, and testing should be designed according to the principles of risk management, that is, according to those variables identified as having a high impact on the quality of the product, and performed according to documented procedures. In-process controls may be based upon monitoring the process or actual sample analysis at defined locations and times.

Sampling methods should be documented to ensure that the sample is representative and clearly labeled. In-process samples should not be returned to production for incorporation into the final batch.

The results of in-process controls should be recorded and should be verified against established process parameters or acceptable tolerances. Work instructions should define the procedure to follow and how to utilize the inspection and test data to control the process.

Where approval to continue with the process is issued within the production department, the specified tests should be performed by trained personnel and the results recorded. Actions should be taken that are supported by the quality unit when the results are outside specified limits.

6.4.7 PACKAGING AND LABELING

Procedures should be employed to protect the quality and purity of the excipient when it is packaged and to ensure that the correct label is applied to all containers. Packaging and labeling operations should be designed to prevent mix ups.

Procedures should be implemented to ensure that the correct labels are printed and issued and that the labels contain the correct information. The information on the label should be indelible. The procedure should also specify that excess labels are immediately destroyed or returned to controlled label storage. Packaging and labeling facilities should be inspected immediately before use to ensure that materials that are not required for the next packaging operation have been removed. The outcome of the inspection should be recorded.

When excipients are labeled on the packaging line, packaged in preprinted bags, or bulk-shipped in tank trucks or railcars, there should be documentation of the process used to ensure the package is properly labeled.

6.4.8 RECORDS OF EQUIPMENT USE

Records of quality-critical equipment use should be retained as controlled records in conformance with *3.6.3 Control of Documented Information*. These records should allow the sequence of cleaning, maintenance, and production activities to be determined.

Records of major equipment use, cleaning, sanitization, and maintenance should show the date, time (if appropriate), product, and batch number of each batch processed in the equipment and the person who performed the cleaning and maintenance.

6.4.9 VALIDATION OF PROCESSES FOR PRODUCTION AND SERVICE PROVISION

The full validation program that is typically performed in the pharmaceutical industry may not always be carried out by the excipient manufacturer; however, product testing alone is not sufficient to reveal variations that may have occurred.

The organization's excipient QMS should provide ongoing evidence that the process is capable of consistently achieving the desired quality outcome based on knowledge of process parameters, excipient attributes, and their interrelationship.

Knowledge of the process may be based on process capability studies, development and scale-up reports, and/or periodic product reviews, etc.

After a significant change, the impact on validation or process capability should be assessed. Where the intent of blending or mixing is to ensure final batch uniformity, it should be demonstrated that such processing achieves a state of homogeneity.

6.5 Inspection and Test Status

Identification and traceability are specific requirements for quality critical raw materials, packaging materials, intermediates, and finished excipients.

Documents that facilitate traceability, e.g., COAs, should be received for each delivery from the supplier as agreed with the customer.

6.5.1 TRACEABILITY

Quality-critical items should be clearly identified and traceable through records. These records should allow traceability of the excipient both upstream and downstream. Identification of raw materials used in batch production processes should be traceable through the batch numbering system or other appropriate system. Identification of raw materials used in excipients produced by continuous processing should indicate the timeframe during which a particular batch of raw material was processed through the plant.

Raw materials, including solvents, are sometimes stored in bulk tanks or other large containers, making precise separation of batches difficult. Nevertheless, the use of such materials should be documented in production records.

Excipient manufacturers should also have adequate knowledge about the origin of any raw materials derived from plant or animal matter (see *6.2.1 Determination of Requirements Related to the Product*).

The lot number of contact or primary packaging used for finished excipient should be recorded in the batch record to facilitate identification of where the lot of the packaging was used.

6.5.2 INSPECTION AND TEST STATUS

There should be a system for identifying the inspection status of raw materials, packaging materials, intermediates, and finished excipients. Although storing materials in identified locations is preferred, any means that clearly identifies the release status is satisfactory. Continuously fed materials may need special consideration in order to satisfy these requirements (see *6.5.1 Traceability*).

6.5.3 LABELING

Labeling for excipient packages is subject to national and international regulatory requirements, which may include transportation and safety measures. At a minimum, labels should include the following:

- The name of the excipient and grade, if applicable
- The excipient manufacturer's name, address of the manufacturing site, and contact information
- The batch number from which the complete batch history can be determined
- Storage conditions, if other than ambient
- Amount of excipient in each container
- Expiry or retest date

6.5.4 PROPERTY BELONGING TO CUSTOMERS AND EXTERNAL PROVIDERS

The excipient manufacturer should establish and maintain procedures for verification, storage, and maintenance of customer-supplied materials intended for incorporation into or the packaging of the excipient designated for that customer. Customer-supplied material that is lost, damaged, or is otherwise unsuitable for use should be documented and reported to the customer. The organization should establish a written agreement with the customer for the acceptable disposition and replacement of lost, damaged, or unsuitable material.

The manufacturer should also make provisions for protecting confidentiality of real and intellectual property that is provided by the customer (e.g., test equipment, test methods, and specifications).

6.6 Preservation of Excipient

The excipient manufacturer should define and justify the conditions for the handling and storage of materials (see *6.5.1 Traceability*) so that their identity, quality, and conformance to specification are not affected within their shelf life or retest/reevaluation interval. Records of storage conditions should be maintained when such conditions may impact the material's quality characteristics. Deviations from specified storage conditions should be assessed and documented.

6.6.1 RAW MATERIAL PACKAGING SYSTEMS

Where a risk assessment has demonstrated that storage and handling of any raw materials may impact excipient quality, the organization should:

- Provide suitable protection against deterioration, contamination with foreign substances, chemical and/or microbiological contamination
- Ensure that identification labels remain legible

6.6.2 HANDLING, STORAGE, AND PRESERVATION

Excipients, intermediates, and raw materials should be handled and stored under appropriate conditions of temperature, humidity, and light so that their identity, quality, and purity are in conformance with the monograph or specification throughout the retest interval or shelf life. Records of storage conditions should be maintained if they are critical for the continuing conformity of the material to specifications. Deviation from specified conditions on material quality should be assessed and documented.

Storage containers should be identified and labeled with their contents.

Outdoor storage of excipients is acceptable, provided that the containers give suitable protection against deterioration or contamination of their contents, identifying labels remain legible, and containers are adequately cleaned prior to opening and use.

Where applicable, deviations from such specified storage conditions should be assessed and documented.

6.6.3 EXCIPIENT PACKAGING SYSTEMS

The selection of excipient packaging systems should be justified by the organization. The excipient packaging system should include the following features:

- Documented specifications shown to provide the excipient with adequate protection against deterioration or contamination during transportation and recommended storage
- Address the excipient's properties and stability
- Incoming inspection and/or testing methods
- Documented evidence that the packaging does not adversely impact quality of the excipient (e.g., packaging is not reactive, additive, or absorptive)
- Compliance with relevant regulatory requirements
- Cleaning procedures, where containers are reused
- Tamper-evident seals, unless written justification demonstrates why such seals are not feasible

Note that a tamper-evident seal is generally feasible. The seal should have a distinct design and possess unique identifying characteristics that are difficult to duplicate. Tamper-evident seals should be traceable to the excipient manufacturer and should not be reusable once the seal is broken.

There should be a procedure for storage and handling that protects containers and closures to minimize the risk of contamination, damage, or deterioration and that will avoid mix ups (e.g., between containers that have different specifications but are similar in appearance). Containers should be stored so as to protect their cleanliness. Where reusable excipient containers are returned, the organization should undertake a risk assessment and establish appropriate controls for their further use. Procedures should ensure all previous labels are removed or completely obliterated.

6.6.4 EXCIPIENT DELIVERY AND DISTRIBUTION

Where contractually specified, protection should extend to include delivery to the final destination. Where controlled conditions are required to maintain excipient quality during transport, suppliers of transport services should be provided with instructions to maintain the required conditions.

For bulk transport in equipment not dedicated to the excipient, verified cleaning procedures should be applied between loadings, and a list of restricted and/or allowed previous cargoes should be supplied to the transport companies. Records of cleaning should be retained.

Excipients should only be supplied within their expiry period, or as otherwise contractually agreed-upon or specified. The time remaining in the expiry and/or retest period should be clear to the customer.

When no expiry period is defined, the excipient should only be supplied within its retest/reevaluation interval as supported by stability data (see *7.3.12 Stability and Expiry/Retest Periods*).

Distribution records of excipient shipments to the initial customer, including identification and traceability, should be maintained and should include, at a minimum:

- Excipient name or unique identifier
- Excipient batch number
- Type of packaging
- Where and to whom the excipient was shipped
- Quantity shipped
- Date of shipment

The manufacturer should maintain the integrity and the quality of the product after final inspection by informing the transport provider of required environmental conditions. Where contractually specified, the excipient manufacturer should ensure this protection extends to delivery to the final destination. Excipients should be supplied only within their expiry and/or retest period.

6.6.5 POST-DELIVERY ACTIVITIES

Deviations that may impact excipient quality and which become known after delivery of the excipient should be evaluated and communicated to customers. The impact of such deviations should be assessed and provisions should be made for return of excipient as necessary.

6.6.6 CONTROL OF MEASURING AND MONITORING DEVICES

Measurement and test equipment, including computerized systems identified as critical to material quality based on risk management, should be calibrated and maintained. This includes in-process instruments as well as test equipment used in the laboratory. The control program should include procedures for the standardization or calibration of instruments and equipment at suitable intervals in accordance with an established, documented program. This program should 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. Calibration standards should be traceable to recognized national or compendial standards as appropriate. Justification should be provided where calibration is not required or where a calibration standard does not exist.

Instruments and equipment not meeting established specifications should not be used, and an investigation should be conducted to determine the validity of the previous results since the last successful calibration. The current calibration status of all quality-critical equipment should be known and verifiable to users through records and/or signage.

7. MEASUREMENT, ANALYSIS, AND IMPROVEMENT

The organization should plan and implement the monitoring, measurement, and improvement activities that are required in order to demonstrate conformity of the excipient to customer requirements and to ensure conformity of the QMS to this chapter. The organization should evaluate opportunities for improvements through the measurement and analysis of product and process trends.

7.1 Monitoring and Measurement of Processes

The excipient manufacturer should identify the tests and measurements necessary to adequately control manufacturing and QMS processes.

Corrective action should be taken to ensure the excipient meets requirements when deviations from planned results occur.

Periodic reviews of key indicators such as process quality attributes, in-process test results, and process failures should be conducted to assess the need for improvements.

7.2 Monitoring and Measurement of Excipient

The organization should establish and provide documentation to support the test methods and procedures used to verify that the excipient meets specifications and that the methods are suitable for their intended purpose.

If the organization claims the excipient is in compliance with a pharmacopeia or an official compendium, then:

- Noncompendial analytical tests used as an alternative to compendial tests should be demonstrated to be at least equivalent to those in the compendia and validated
- The excipient should comply with applicable monographs, general chapters, and notices
- Responsibility for monitoring those pharmacopoeias or official compendia should be assigned

7.2.1 CHANGE CONTROL

There should be a written procedure, based on risk management, for determining which changes to communicate to customers, as well as a mechanism for communicating such changes. Significant changes should be communicated with sufficient notice prior to implementation as is reasonably practical to customers (see *6.2.3 Customer Communication*) and, as applicable, to regulatory authorities. The customer should be informed prior to the first shipment of the excipient after the change is implemented. Documentation generated for change control should be retained (see section *3.6.3 Control of Documented Information*).This also applies to discontinuation of manufacture of an excipient.

Risk assessment should be used to evaluate the potential impact of proposed changes on excipient quality. The level of formality of the evaluation should be commensurate with the level of risk to excipient quality as reflected in the composition of the excipient. Also see ⟨1195⟩.

7.2.2 FINISHED EXCIPIENT TESTING AND RELEASE

Tests for verification of excipient quality should be performed and recorded to confirm that the excipient conforms to documented specifications. There should be a procedure to ensure the evaluation and approval of the appropriate manufacturing and test documentation prior to the release of the finished excipient by the quality unit.

Assurance that excipients conform to documented specifications may be achieved through the results of in-process testing or other process control records, or periodic finished product testing other than on the finished excipient sample if it can be shown that such testing or control results would be achieved through finished excipient sampling and testing.

7.2.3 CONTROL OF NONCONFORMING MATERIALS

Any raw material, intermediate, or finished excipient not meeting its specifications should be clearly identified and controlled to prevent inadvertent use or release for sale. Procedures and records should be maintained for the evaluation and appropriate disposition of nonconforming raw materials, intermediates, and excipients.

Nonconformance should be investigated according to a documented procedure in order to identify the root cause and to assess the potential impact on other batches and products as well as on processes and activities. The investigation should be documented, and corrective action should be taken to prevent recurrence as sections *7.2.5 Investigation of Nonconforming Finished Excipient* and *7.5.2 Corrective Action* indicate.

There should be procedures to prevent shipment of excipients that would be unacceptable to certain customers, when a customer-specific requirement is not met.

Note that in certain circumstances a particular customer may have additional specification requirements beyond the general sales specification(s) for material manufactured using the same equipment and process as the general material. If material manufactured in compliance with this chapter meets requirements of the general sales specification(s) but not an individual customer specification(s), it may still be sold to those customers whose specification(s) it does meet.

For a nonconforming excipient that is already in distribution, there should be a documented procedure defining how the retrieval should be conducted and recorded (i.e., market withdrawal or recall). The effectiveness of the arrangements for recalls should be evaluated at regular intervals, e.g., by conducting a traceability exercise or "mock" recall.

7.2.4 RETURNED EXCIPIENTS

There should be a procedure(s) for the evaluation, holding, testing, and reprocessing or reworking of returned excipients. Returned excipients should be identified and controlled to prevent inadvertent use or release for sale until a documented evaluation of their quality has been completed by the quality unit.

When the intent is to make a returned excipient available for sale to another pharmaceutical customer, the evaluation should consider conformance to the labeled storage and/or transportation conditions throughout the supply chain. The excipient should not be released if there is any reason to believe that container integrity or excipient quality may have been compromised.

Records for returned excipients should be maintained and should include the excipient name, batch number, reason for return, identity of the organization that returned the excipient, quantity returned, and ultimate disposition of the returned excipient. The quality unit should determine and record the ultimate disposition of returned excipient.

7.2.5 INVESTIGATION OF NONCONFORMING FINISHED EXCIPIENT

Failure of a batch to meet specification for the grade being produced, including failure to meet a customer-specific requirement, should be investigated using a procedure to identify the root cause, impact on other batches and products, and appropriate corrective and preventative actions. These investigative principles apply to customer complaints (see *6.2.4 Customer Complaints*). Once the root cause is identified, corrective and/or preventative action should be taken to bring the process back into a state of control or to improve the process capability. A record of each incidence of nonconformance should be documented and maintained. The potential impact of any change on validation should be assessed.

7.2.6 DISPOSITION OF NONCONFORMING FINISHED EXCIPIENT

Upon the conclusion of the investigation as described in *7.2.5 Investigation of Nonconforming Finished Excipient*, the quality unit should assign one of the following final dispositions to the finished excipient:

- Released as an excipient grade for which all established requirements are met
- Reprocessed or reworked (see *7.2.7 Reprocessing* or *7.2.8 Reworking*)

- Released as a nonpharmaceutical grade material or destroyed
- Accepted by customer with their agreement to accept any risk

7.2.7 REPROCESSING

Reprocessing should only occur when it has already been documented that the excipient may be processed to conform to the monograph or specification using the same process and equipment. The organization should maintain records of reprocessing activities to ensure traceability of the reprocessed material into the finished excipient.

7.2.8 REWORKING

Reworking is a change under the provisions of change control in this chapter (see *6.2.5 Changes to Requirements for Products and Services*) and should only be conducted following a documented review of risk to excipient quality that is approved by the quality unit.

When performing the risk assessment, a documented investigation should be completed and the following considered, unless otherwise justified and documented:

- Additional testing to monitor and control the reworking
- Suitable acceptance criteria for the reworked excipient
- Search for new impurities that may be introduced as a result of reworking
- Records and traceability to the original batches
- Impact on stability or the validity of the retest/reevaluation interval
- Composition profile changes as a result of reworking
- Performance of the excipient
- Additional controls needed to minimize the risk to excipient quality
- Need to notify the customer of reworked excipient and have documentation that the customer has agreed to accept the material

Equivalence of the quality of reworked material to original material should also be evaluated and documented to demonstrate that the batch will conform to established specification and characteristics. The evaluation should be approved by the quality unit. Records of reworking should be maintained.

When blending is used for reworking, the resultant product should demonstrate the same chemical and physical properties and performance characteristics as routine production. Blending batches that are contaminated or adulterated to reduce the contamination or adulteration below an acceptable or detectable limit is not acceptable under this chapter.

7.3 Performance Evaluation

7.3.1 GENERAL

The organization should evaluate the performance and the effectiveness of the QMS. The organization should plan and implement the monitoring, measurement, and improvement activities required to ensure conformity of the QMS to this chapter. The organization should retain appropriate documented information as evidence of the results.

7.3.2 CUSTOMER SATISFACTION

The organization should assess customer satisfaction. The assessment should support continual improvement.

Note that such measurements may include investigation of responses to customer complaints, return of excipients, and customer feedback.

7.3.3 ANALYSIS OF DATA

The excipient manufacturer should develop methods for evaluating the effectiveness of its QMS and use those data to identify opportunities for improvement.

Excipient manufacturer should define methods for evaluating:

- The effectiveness of its QMS
- The ability to consistently produce conforming excipients
- Excipient nonconformance with this chapter, customer complaints, deviations, etc.
- Supplier nonconformance

The organization should use results and trends to identify opportunities for improvement.

7.3.4 ANALYSIS AND EVALUATION

Best practice is to continuously conduct review of key indicators such as product quality attributes, customer complaints, and product nonconformities to assess the need for improvement.

The organization should identify opportunities for improvements through the measurement and analysis of product and process trends.

7.3.5 LABORATORY CONTROLS

Measures should be taken to maintain data integrity at all times. The excipient manufacturer should have procedures in place to ensure data is authentic, legible, complete, original, contemporaneously recorded, and accurate; that it can be traced to its source; and that it is readily available.

Laboratory controls should include complete data derived from tests necessary for ensuring conformity with specifications and standards including:

- Data to enable identification and traceability of samples that are used to determine batch status, by using a batch number or other distinctive code and the date the sample was taken
- Record of sample preparation showing conformance with test requirements
- Traceability using a statement referencing each test method used along with record of raw data secured during each test, including graphs, chromatograms, charts, and spectra from laboratory instrumentation; identified to show the specific material and batch tested
- A record of calculations performed in connection with the test
- Test results and how they compare with established specifications
- A record of the person who performed each test and the date(s) the tests were performed

7.3.6 Reference Reagents and Standards

Where used, certified reference reagents and primary reference standards should be appropriately stored and need not be tested upon receipt, provided that a COA from the supplier is available. Secondary reference standards should be appropriately prepared, identified, tested, approved, and stored. There should be a documented procedure for the qualification of secondary reference standards against primary reference standards. The reevaluation period should be defined for secondary reference standards, and each batch of standards should be periodically requalified in accordance with a documented protocol or procedure.

The procedures for handling of standards, including those prepared in-house, and reagents should include:

- Record of preparation, identification, testing, approval, and storage
- Labeling, including for purchased items, should include name, concentration, date of first use or date of preparation, and the assigned expiration or standardization date
- Provisions for the receipt, storage, and use of primary reference standards
- When the reagent or test solution is purchased, traceability information should be recorded

7.3.7 Out-of-Specification Test Results

Where the finished material is tested to confirm it is suitable for sale as an excipient and the result indicates it is nonconforming, the organization should conduct a thorough documented investigation of all out-of-specification (OOS) test results, starting with a prompt laboratory investigation, according to a documented procedure. The findings of the investigation, including conclusions and follow up actions, should be recorded.

Retest sample results may only be used to replace the original test result if a documented investigation concludes that the original result is erroneous due to an assignable root cause.

The OOS procedure should provide detailed steps for conducting an investigation and criteria that allow for a retest sample. The procedure should define appropriate provisions for investigation of original test results, including but not limited to:

- Criteria for retesting the original sample
- Criteria for resampling the finished material
- The need to perform an investigation of manufacturing to determine the cause of the failure when the laboratory investigation yields no conclusive assignable cause that invalidates the original result

The results of the OOS investigation should be used to determine batch disposition.

When statistical analysis is used, both the original and retest data must be included. The OOS procedure should define which statistical techniques are to be used and under what circumstances. These same principles apply when the sample is suspected of not being representative of the material from which it was taken.

7.3.8 Retained Samples

A representative sample of each batch of the excipient should be retained unless the nature of the excipient makes this impractical and this fact is justified and documented. The retained sample retention period should be justified.

Retained samples should be stored in a secure location, readily retrievable, and under conditions consistent with the storage conditions specified for the excipient.

Unless otherwise justified and documented, the sample size should be at least twice the amount required to perform complete specification testing and maintained in a packaging format that is equivalent to or more protective than the commercial packaging system.

7.3.9 Certification of Analysis

The organization should provide certificates of analysis to the required specification for each batch of excipient (see *Bulk Pharmaceutical Excipients—Certificate of Analysis* ⟨1080⟩).

The COA should include, at a minimum:

- Excipient name (trade name), and if applicable, grade, and compendial name with compendial reference, or reference to the excipient specification
- Organization's name, contact information, and identity of the site of manufacture. If the site of manufacture is not detailed on the COA, then this information should be communicated separately
- Date of manufacture

- Batch number
- Expiration date or retest date, and if previously retested, the date it was retested
- List of each test performed
- Reference the test procedure
- The acceptance limits or criteria
- The results with numerical units preferably or statement of conformance to the required specification, as appropriate
- Statement of compliance to GMP as defined by this chapter (this may be otherwise communicated with the customer)
- Analytical results representative of the batch and if not based on testing of a sample of the finished excipient, the basis of the results should be communicated to the customer
- Name and title of person whose physical signature appears on the COA or electronic signature statement
  Note that it is a responsibility of the excipient purchaser to satisfy their expectation if an electronic signature is used. It is advisable to include environmental storage conditions on a COA when other than ambient.

7.3.10 EXCIPIENT COMPOSITION

Unless otherwise justified, the organization should develop an excipient composition profile to monitor composition and to control manufacturing processes so that the excipient composition is maintained within appropriate ranges. Limits for excipient composition, including upper limits for impurities, should be established based on an understanding of safety considerations, regulatory requirements, official compendia, and customer requirements. Also see ⟨1195⟩.

7.3.11 IMPURITIES

Excipient manufacturers should follow applicable regulatory requirements and recommendations to help pharmaceutical manufacturers, repackers, and other suppliers of excipients prevent the use of excipients that are contaminated. These requirements and recommendations, along with other appropriate measures under current good manufacturing practice (cGMP), are vital to prevent further consumer poisonings.

Excipient manufacturers should conduct documented risk assessments to determine whether the excipient specifications should include tests and limits for impurities, based on safety or the expectations of interested parties (see *3.2 Understanding the Needs and Expectations of Interested Parties*). Where needed, limits and methods should be established such as required for residual solvents (*Residual Solvents* ⟨467⟩), elemental impurities (*Elemental Impurities—Limits* ⟨232⟩), and other chapters in the *USP-NF*.

Consideration should be given to the following:

- Microbiological bioburden (see *Microbiological Examination of Nonsterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use* ⟨1111⟩
- Contaminants originating from raw materials of natural origin, e.g., mycotoxins, pesticide residues

Technically unavoidable visible particles cannot be fully excluded from some excipients. The excipient manufacturer should implement mitigation strategies based on documented risk assessment to maintain the occurrence of such technically unavoidable particles within the capability of processes. See IPEC Technically Unavoidable Particle Profile (TUPP) Guide, 2015 (*https://www.gmp-compliance.org/files/guidemgr/tuppguide2015-1539615522.pdf*).

7.3.12 STABILITY AND EXPIRY/RETEST PERIODS

The stability of excipients is an important factor in the overall quality of the drug product.

The stated stability of the excipient should be demonstrated through at least one of the following methods:

- Historical data (for excipients that have been on the market for a long time)
- Stability studies

An expiry or retest/reevaluation interval for the excipient should be determined, justified, and communicated to the customer. Where a stability study is used to demonstrate excipient shelf life, the details of the study should be documented and periodically confirmed.

In some cases, the excipients are very similar to others within a product group; minor quantitative differences of some of the excipient components may be the only significant variation from one product to another. In such cases, a model product approach (i.e., bracketing and matrixing approach) may be appropriate for assessment of the stability of similar excipients. The selection of excipients used for such studies should be scientifically sound and documented. Data from stability studies of these model products can be used to determine the stability for similar products.

7.4 Internal Audit

The excipient manufacturer should carry out a comprehensive system of planned and documented internal quality audits.

Audits should be conducted by qualified individuals, independent of the area being audited, according to documented procedures. Selection of auditors and conduct of audits should ensure objectivity and impartiality of the auditors.

Audits and audit frequency criteria should be scheduled based on a risk management analysis. Schedules should be based on findings from previous audits, performance measures (see *7.3.3 Analysis of Data*), and the potential impact of the activity to finished excipient quality.

Audit scope should include, at a minimum, the following:

- Determination of the effectiveness of processes and quality activities
- Compliance with procedures and processes described by the QMS
- Complaints, out-of-trend reports, and/or OOS reports

- Provisions for follow-up actions
- Positive findings that support the effective implementation of GMP
- Deficiencies that need corrective and/or preventive action

Audit results should be documented and discussed with management personnel having responsibility in the area(s) audited. Management personnel responsible for the area(s) audited should take corrective action and/or preventive action without undue delay on each nonconformance found.

See the *Appendix: Auditing Considerations* for more details for assistance in establishing an internal audit program.

7.5 Improvement

7.5.1 CONTINUOUS IMPROVEMENT

The excipient manufacturer should take proactive measures to continuously improve manufacturing and QMS processes. To identify opportunities for continual improvement, analysis of the following performance indicators may be considered:

- Causes of nonconforming product
- Results of internal and external audits
- Customer returns, complaints, and other feedback
- Process and operational failures

7.5.2 CORRECTIVE ACTION

The excipient manufacturer should carry out corrective actions based on documented procedures that address:

- Determining the root causes of nonconformities
- Definition of corrective actions including assignment of responsibilities and timelines for implementation
- Ensuring that corrective actions are implemented and effective
- Procedures resulting from corrective action

7.5.3 PREVENTIVE ACTION

The excipient manufacturer should establish procedures for:

- Initiating preventive actions, including assignment of responsibilities and timelines for implementation. The investigation should be at a sufficiently detailed level commensurate with the risk identified (see *7.2.5 Investigation of Nonconforming Finished Excipient*).
- Ensuring that preventive actions are implemented and effective
- Implementing and recording changes in procedures resulting from preventive action

▲ (USP 1-Dec-2024)

Change to read:

GLOSSARY

The terms below are defined as used in this chapter. Wherever possible, definitions used by the International Conference on Harmonization have been used as the basis for the glossary.

Acceptance criteria: Numerical limits, ranges, or other suitable measures of acceptance for test results.

Active pharmaceutical ingredient (API): Any substance or mixture of substances that is intended to be used in the manufacture of a drug product and that, when used in the production of a drug, becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of humans or animals.

Adulterated material: A material that either has been contaminated with a foreign material or has not been manufactured using GMP. This does not pertain to a material that simply does not meet physical or chemical specifications.

Batch (Lot): A specific quantity of material produced in a process or series of processes so that it can be expected to be ▲uniform in attributes and quality within specified limits▲ (USP 1-Dec-2024) . In the case of continuous processes, a batch may correspond to a defined fraction of the production. The batch size can be defined either by a fixed quantity or by the amount produced in a fixed time interval.

Batch number (Lot number): A unique combination of numbers, letters, and/or symbols that identifies a batch and from which the production and distribution history can be determined.

Batch process: ▲A manufacturing process or processing step that produces the excipient from a discrete supply of raw material that is present before the completion of the reaction.▲ (USP 1-Dec-2024)

Batch record: Documentation that provides a history of the manufacture of a batch of excipient.

Blending (Mixing): Intermingling different conforming ▲batches▲ (USP 1-Dec-2024) into a homogeneous lot.

Calibration: The demonstration that a particular instrument or measuring device produces results within specified limits by comparison with those produced by a reference or traceable standard, over an appropriate range of measurements.

▲▲ (USP 1-Dec-2024)

Certificate of analysis: A document listing the test methods, specification, and ▲test results from samples representative of the batch or in-process data from the material to be delivered.▲ (USP 1-Dec-2024)

Commissioning: ▲Verification that the equipment is suitable for use in a controlled manner. A systematic approach to the start-up and turnover of facilities, systems, and equipment to end-users, and ensuring that user requirements and design specifications are met.▲ (USP 1-Dec-2024)

Contamination: The undesired introduction of impurities of a chemical or microbiological nature or foreign matter into or onto a raw material, intermediate, or excipient during production, sampling, packaging or repackaging, storage, or transport.

Continuous process ▲or processing▲ (USP 1-Dec-2024) **:** A process that continuously produces material from a continuing supply of raw material.

▲**Corrective action:** Action to eliminate the cause of a detected nonconformity or other undesirable situation. Note that corrective action is taken to prevent recurrence, whereas preventive action is taken to prevent occurrence.▲ (USP 1-Dec-2024)

Cross-Contamination: Contamination of a material or product with another material or product.

Customer: The organization ▲that purchases▲ (USP 1-Dec-2024) the excipient▲▲ (USP 1-Dec-2024) ·

Deviation: Departure from an approved instruction or established standard.

▲▲ (USP 1-Dec-2024)

Drug ▲▲ (USP 1-Dec-2024) **product:** The dosage form ▲intended for use by a patient▲ (USP 1-Dec-2024) ·

Excipient: Substances other than the API that have been appropriately evaluated for safety and are intentionally included in a drug delivery system.

Expiry (Expiration) date: The date designating the time during which the excipient is expected to remain within specifications ▲while in the unopened container▲ (USP 1-Dec-2024) and after which it should not be used.

▲**Failure mode and effects analysis (FMEA):** A structured approach to discovering potential failures that may exist within the design of a product or process. Failure modes are the ways in which a process can fail. Effects are the ways that these failures can lead to waste, defects, or harmful outcomes for the customer.

Hazard analysis and critical control point (HACCP): A systematic approach to the identification, evaluation, and control of safety hazards.▲ (USP 1-Dec-2024)

Impurity: ▲An unintended component of an excipient that is present as a consequence of the raw materials, excipient manufacturing process, or excipient degradation.▲ (USP 1-Dec-2024)

In-Process control/Testing: Checks performed during production to monitor and, if appropriate, to adjust the process and/or to ensure that the intermediate or excipient conforms to its specification.

Intermediate: Material that must undergo further ▲processing to become the excipient.▲ (USP 1-Dec-2024)

Lot: See *Batch*.

Manufacturer: ▲The organization that performs final production steps and release of the excipient.

Manufacturing process: All steps necessary to produce an excipient from raw materials.▲ (USP 1-Dec-2024)

Master production instruction (Master production and control record): Documentation that describes the manufacture of the excipient from raw material to completion.

Material: A general term used to denote raw materials (starting materials, reagents, and solvents), process aids, intermediates, excipients, packaging, and labeling materials.

Model product: A product that represents a group of similar products with respect to composition, functionality, or specification.

Mother liquor: The residual liquid that remains after crystallization or isolation processes.

Packaging material: A material intended to protect an intermediate or excipient during storage and transport.

Production: Operations involved in the preparation of an excipient from receipt of materials through processing and packaging of the excipient.

▲**Product life cycle:** All phases in the life of the product from the initial development through marketing until the product's discontinuation.

Protocol: A detailed plan describing the conduct of a study.▲ (USP 1-Dec-2024)

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

Quality control: Checking or testing that specifications are met.

Quality-Critical: Describes a material, process step or process condition, test requirement, or any other relevant parameter that directly influences the quality attributes of the excipient and that must be controlled within predetermined criteria.

▲**Quality unit:** An organizational unit independent of production which fulfils both quality assurance (QA) and quality control (QC) responsibilities. This can be in the form of separate QA and QC units or a single individual or group, depending upon the size and structure of the organization.▲ (USP 1-Dec-2024)

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

Raw material: A general term used to denote starting materials, reagents, and solvents intended for use in the production of intermediates or excipients. ▲Raw material and starting material are not equivalent as starting material has a different meaning in a regulatory context.▲ (USP 1-

Dec-2024)

Record: A document stating results achieved and/or providing evidence of activities performed▲, e.g., training records, executed batch production and control records, executed batch packaging records, validation reports, laboratory test results forms, laboratory notebooks, equipment logbooks, memos, and emails. ▲ (USP 1-Dec-2024) The medium may be paper, magnetic, electronic or optical, photographic, or another medium, or a combination thereof.

Reevaluation date (Retest date): ▲ The date when a specific batch of excipient must be re-examined to ensure it is still suitable for its intended use.

Reevaluation interval: The duration, normally expressed in months or years, from the date of manufacture, throughout which the excipient should continue to conform to the specification and after which should be tested to confirm it continues to meet specification.▲ (USP 1-Dec-2024)

Reprocessing: Repetition of an activity that is a normal part of the manufacturing process and that has been documented previously.

Retrieval: Process for the removal of an excipient from the distribution chain.

Reworking: Subjecting previously processed material that did not conform to standards or specifications to processing steps that differ from the normal process.

▲**Risk:** The combination of the probability of occurrence of harm and the severity of that harm.

Risk assessment: A systematic process of organizing information to support a risk decision to be made within a risk management process. It consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards.

Quality risk management (QRM): The systematic application of quality management policies, procedures, and practices to the tasks of assessing, controlling, communicating, and reviewing risk.

Service provisions: Wide range of activities on which the performance of the manufacture and quality of the excipient depends.

Shelf life: The length of time during which the excipient is required to meet specification (see also *Expiry date*, *Reevaluation interval*, and *Reevaluation date*).

Site: A defined location of the equipment in which the excipient is manufactured. It may be within a larger facility. A change in site may be to a different part of the existing facility, but in a different operational area, or to a remote facility including a contract manufacturer.▲ (USP 1-Dec-2024)

Specifications: List of tests, references to analytical procedures, and appropriate acceptance criteria that are numerical limits, ranges, or other criteria for the tests described for a material.

Stability: Continued ▲conformance▲ (USP 1-Dec-2024) of the excipient to its specifications.

▲**Supplier:** Person or company providing materials on request. Suppliers may be distributors, manufacturers, traders, etc.

Supply chain: All steps in the entire chain of distribution starting from the point at which an excipient is transferred outside the control of the original manufacturer's material, to a management system downstream, to the final user of the excipient.▲ (USP 1-Dec-2024)

Top Management: Person or group of people who direct and control an organization at the highest level. The highest level can be at either the site level or the corporate level and will depend on the way in which the quality management system is organized.

Traceability: Ability to determine the history, application, or location that is under consideration (e.g., origin of materials and parts, processing history, or distribution of the product after delivery).

Validation: A documented program that provides a high degree of assurance that a specific process, method, or system will consistently produce a result meeting predetermined acceptance criteria.

▲**Yield, theoretical:** The quantity of material that would be produced at any appropriate step of production, based upon the quantity of material to be used, in the absence of any loss or error in actual production.▲ (USP 1-Dec-2024)

Change to read:

APPENDIX

Auditing Considerations

INTRODUCTION

Many excipients are used in food, cosmetic, and industrial products as well as in pharmaceuticals. Thus, environmental conditions, equipment, and operational techniques employed in excipient manufacture are often those of the chemical industry as opposed to the pharmaceutical industry. Chemical processes can produce impurities from side reactions. Careful process control is therefore essential to minimize levels of impurities and ▲the risk of introducing▲ (USP 1-Dec-2024) contamination ▲from processing equipment and the environment.▲ (USP 1-Dec-2024)

Excipients are often manufactured on a large scale, using continuous processing and automated process controls. ▲Even batch processing often involves a continuous process operation such as drying, grinding, distillation, etc.▲ (USP 1-Dec-2024) Production equipment and processes vary depending on the type of excipient being produced, the scale of production, and the type of operation (e.g., batch versus continuous process).

This appendix is intended as an aid in preparing for an audit of an excipient manufacturer. Both external and internal auditors (see also ▲*7.4 Internal Audit*▲ (USP 1-Dec-2024)) will find this appendix useful in identifying the significant issues with respect to GMP and quality that

require examination. This section will assist excipient manufacturers in identifying key deliverables when adopting the GMP standards listed in the other sections of this chapter; in planning an audit, it will also help to verify the quality of the excipient manufacturing process and the manufacturer's QMS.

GMP PRINCIPLES

Control of Impurities and Contamination: In general, the pharmaceutical customer does not perform further chemistry or purification steps on the excipient; it is used as purchased. Consequently, impurities present in the excipient are likely to be present in the drug product. Although dosage form manufacturers have some control over excipient quality through specifications, excipient manufacturers have greater control over the physical characteristics, quality, and presence of impurities ▲and contaminants▲ (USP 1-Dec-2024) in the excipients they produce.

External contamination of the excipient can arise from the manufacturing environment. However, chemical processes used to manufacture excipients are often performed in closed systems that afford protection against such contamination, even when the reaction vessels are not located in buildings. The external environment may require suitable controls to avoid potential contamination wherever the excipient or in-process material is exposed.

Excipient Properties and Functionality: Excipients are frequently used in those types of drug products for which physical characteristics, such as particle size, may be important. Although the manufacturer of the finished dosage form is primarily responsible for identifying the particular physical characteristics needed, it is also the responsibility of the excipient manufacturer to control excipient manufacturing processes to ensure consistent conformity to excipient specifications ▲and excipient composition. Caution should be taken whenever a purposeful change in the composition of the excipient occurs as this may impact excipient performance in certain formulations.▲ (USP 1-Dec-2024) Wherever possible, consideration should be given to the end use of the excipient. This is particularly important if the excipient is a direct component of a sterile drug product or one that is claimed to be ▲pyrogen-tested or▲ (USP 1-Dec-2024) pyrogen-free.

Consistency of Manufacture and Change Control: A thorough understanding of the manufacturing process and effective control of change can best ensure consistency of excipient quality from batch to batch. Implementation of changes may also have consequences for registration filings with regulatory agencies.

Changes in excipient manufacturing processes may result in changed physical or chemical properties of the excipient that are evident only during subsequent ▲excipient▲ (USP 1-Dec-2024) processing or in the finished dosage form. This is particularly important in the context of the pharmaceutical product approval process where bioequivalence comparisons are made between pivotal, clinical trial batch (*bio batch*) production and commercial scale-up batches. Changes made to the excipient supplied for the commercial product from the excipient supplied for the bio batch should not affect the quality and performance of the commercial drug product. Scale-up of excipients to commercial production may involve several stages, and data may be required to demonstrate consistency between batches through the scale-up process.

Traceability: Traceability of batch-related records to facilitate investigations and retrieval of product is also a key requirement of GMP.

APPLICATION OF GMP PRINCIPLES

It is the responsibility of the excipient manufacturer to designate and document the rationale for the point in the manufacturing process at which appropriate GMP are to be applied. From this point on, ▲the principles of this general chapter▲ (USP 1-Dec-2024) should be applied. The manufacturer should apply a level of GMP to each ▲subsequent▲ (USP 1-Dec-2024) manufacturing stage commensurate with the importance of that step in ensuring product ▲quality.▲ (USP 1-Dec-2024) This may be demonstrated by means of the use of a risk assessment ▲technique▲ (USP 1-Dec-2024) (e.g., HACCP, FMEA).

The stringency of GMP in excipient production should increase as the process proceeds from early manufacturing to the final stages ▲of▲ (USP 1-Dec-2024) purification and packaging. Physical processing ▲that occurs after final purification ▲ (USP 1-Dec-2024) (e.g., granulation, coating, or physical manipulation of particle size such as milling or micronizing) as well as chemical processing of excipients should be conducted at least to the standards suggested by this chapter.

It should be recognized that not all intermediates may require testing. An excipient manufacturer should, however, be able to identify critical or key points in the manufacturing process where selective intermediate sampling and testing are necessary in order to monitor process performance.

GENERAL AUDITING CONSIDERATIONS

Audits of an excipient operation will be influenced by the purpose of the audit and the intended use of the excipient. The key stages of a production process should be examined to determine whether the manufacturer controls these steps so that the process performs consistently. ▲A general excipient GMP▲ (USP 1-Dec-2024) audit should assess the excipient manufacturer's capability to deliver a product that consistently meets established specifications ▲and consistent composition in substantial conformance to this general chapter.▲ (USP 1-Dec-2024)

The audit team may consist of engineers, laboratory analysts, purchasing agents, computer experts, maintenance staff, and other personnel as appropriate to the scope and purpose of the audit. External auditors must respect the confidentiality of the manufacturer's processes and other disclosures.

▲It should be appreciated that in global organizations some functions may be centralized and hence may not be auditable at every manufacturing location (e.g., stability programs, supplier approval, IT related activities, etc.).▲ (USP 1-Dec-2024)

An audit should focus on the quality-critical processing steps that are necessary for producing an excipient that meets established physical and chemical criteria. These steps should be identified and controlled by the excipient manufacturer. Quality-critical processing steps can involve a number of unit operations or unit processes. Quality-critical steps can include, but are not limited to, the following:

- Phase changes involving the desired molecule, solvent, inert carrier, or vehicle (e.g., dissolution, crystallization, evaporation, drying, sublimation, distillation, or absorption)
- Phase separation (e.g., filtration or centrifugation)
- Chemical changes involving the desired molecule (e.g., removal or addition of water of hydration, acetylation, or formation of a salt)
- Adjustments of the solution containing the molecule (e.g., pH adjustment ▲or viscosity modification▲ (USP 1-Dec-2024))
- Precise measurement of added excipient components, in-process solutions, and recycled materials (e.g., weighing or volumetric measurements)
- Mixing of multiple components
- Changes ▲made to▲ (USP 1-Dec-2024) surface area, particle size, or batch uniformity (e.g., milling, agglomeration, or blending)

AUDIT CHECK POINTS

A good approach for an excipient plant audit is a review of the following areas ▲using a physical walkthrough of manufacturing and supporting processes following material flow:▲ (USP 1-Dec-2024)

- Nonconformities—such as the rejection of a batch that did not meet specifications, ▲▲ (USP 1-Dec-2024) return of a product by a customer, or retrieval ▲(i.e., recall)▲ (USP 1-Dec-2024) of a product. The manufacturer should have determined the cause of the nonconformity, prepared a report of the investigation, and initiated and documented subsequent corrective action. Records and documents should be reviewed to ensure that nonconformities are not the result of a poorly developed or inconsistent process
- Customer complaint files—such as reports that some aspect of the product is not entirely suitable for use, because such problems may be caused by impurities or inconsistencies in the excipient manufacturing process
- Change control logs—to ascertain whether ▲the quality unit participates in the review and approval process and▲ (USP 1-Dec-2024) the company evaluates its significant changes to decide whether the customer and/or regulatory authority should be notified
- Nonconforming products meeting or Material Review Board documents and/or equivalent records that demonstrate that the disposition of nonconforming product is ▲approved by the quality unit and executed▲ (USP 1-Dec-2024) in an appropriate manner by responsible individuals
- Master formula and production records for frequent revisions that may reveal problems in the excipient production process
- Evidence for the presence of unreacted intermediates and solvent residues in the finished excipient
- Materials management systems, to ensure adequate control over nonconforming materials so that they cannot be sold to customers or used in manufacturing without authorization ▲by the quality unit▲ (USP 1-Dec-2024)
- Review of a process flow diagram, to aid understanding of the various processing stages. The critical stages and sampling points should be identified as part of the review of the processing records
- Review of contamination control measures▲, including environmental contaminants
- Relevant documented risk assessments under a quality risk management program
- Data integrity aspects with an emphasis on each record being uniquely identified and computer audit trails enabled
- Training records
- Safety issues

For manufacture of the finished excipient,▲ (USP 1-Dec-2024) it is appropriate to consider the following risk factors:

- The type of ▲processing equipment▲ (USP 1-Dec-2024) (e.g., open or closed). Enclosed systems in chemical plants often are not closed when they are being charged and/or when the final product is being emptied. ▲▲ (USP 1-Dec-2024)
- The form of the material (e.g., wet or dry)
- The stage of processing and use of the equipment and/or area (e.g., multipurpose or dedicated)
- Continuous versus batch production

▲Packages and labeling processing should evaluate the adequacy of measures taken to prevent contamination and cross-contamination of materials in these operations.▲ (USP 1-Dec-2024)

DOCUMENTATION AND RECORD REVIEW

Documentation required for the early steps in the process need not be as comprehensive as in the latter stages of the process. It is important that a chain of documentation exist and that it be complete when the following is the case:

- The excipient can be identified and quantified for processes ▲to produce a significant structural fragment.▲ (USP 1-Dec-2024) For batch production, a theoretical mass balance may also be established with appropriate limits, because deviations from tolerance are a good indicator of a loss of ▲process▲ (USP 1-Dec-2024) control
- An impurity or other ▲deleterious▲ (USP 1-Dec-2024) substance likely to adversely affect the ▲excipient performance or functionality or identity▲ (USP 1-Dec-2024) of the molecule is identified, and subsequent attempts are made to remove it

As chemical processing proceeds, a chain of documentation should be established that includes the following:

- A documented process
- The identification of critical processing steps
- Appropriate production records▲, tracing all intermediates through to the finished excipient
- ▲ (USP 1-Dec-2024)
- Records of raw materials used
- Comparison of test results against ▲established▲ (USP 1-Dec-2024) standards ▲or acceptance criteria
- Overview of any subcontracted operations, including those performed by a contract testing lab▲ (USP 1-Dec-2024)

If significant deviations from the normal manufacturing process are recorded, there should be evidence of suitable investigations and a review of the ▲impact to▲ (USP 1-Dec-2024) quality of the excipient. Complete documentation should be continued throughout the remainder of the process for quality-critical processing steps until the excipient is packaged and ▲shipped to the customer.▲ (USP 1-Dec-2024) The batch should be homogeneous within the manufacturer's specifications ▲or otherwise identified.

To ▲ (USP 1-Dec-2024) promote uniformity in excipient GMP inspections, the following basic requirements should be established:

- Assignment of a unique batch number to the excipient, enabling it to be traced through manufacture to release and certification
- Suitable controls for the preparation of a batch record for batch processing and/or a production record, log sheet, or other appropriate documentation for continuous processing
- Demonstration that the batch has been prepared using GMP guidelines from the processing point at which excipient GMP have been determined to apply
- Confirmation that the batch is not combined with material from other batches for the purpose of either hiding or diluting an adulterated batch
- Records showing that the batch has been sampled in accordance with a sampling plan that ensures a representative sample of the batch ▲and poses minimal risk of contamination to the batch▲ (USP 1-Dec-2024)
- Records showing that the batch has been analyzed using scientifically established test methods designed to ensure that the product meets established standards, specifications, and ▲other applicable▲ (USP 1-Dec-2024) characteristics
- Stability data adequate to support the intended period of use of the excipient. These data can be obtained from historical data, from actual studies on the specific excipient, or from applicable model product studies that can reasonably be expected to simulate the performance of the specific excipient.▲ For those that degrade under storage, stability indicating methods should be developed and used. Data and the stability test program should be made available during audit (customer or certification).▲ (USP 1-Dec-2024)

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