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Draft Standard for
Pharmaceutical Excipients

Good Manufacturing Practices (GMP) for Pharmaceutical Excipients

1 General

1.1 Introduction

The principles outlined in this Standard provide a comprehensive basis for the quality management system used in the manufacture of pharmaceutical excipients. Implementation of these principles shall result in the achievement of three main objectives:

- a) achieve excipient realization – the organization shall implement and maintain a system that delivers excipients with the quality attributes necessary to meet the requirements and expectations of customers, pharmaceutical users, and regulatory authorities,
- b) establish and maintain a state of control – the organization shall ensure the manufacture and supply of excipients is in accordance with this Standard, thus providing customers with some assurance of continued suitability and reliability of supply, and
- c) facilitate continual improvement – the organization shall collect objective evidence to continually develop and enhance the application of these quality management system principles to further assure excipient consistency.

1.2 Scope

This Standard is intended to define Good Manufacturing Practices (GMP) for excipient manufacture for use in drug products. It sets minimum requirements for GMP applicable to all excipients.

This Standard includes the critical elements of a quality management system for excipient manufacture and the GMP principles in the *IPEC-PQG Good Manufacturing Practices Guide for Pharmaceutical Excipients*.

NOTE – Auditing excipient manufacturers ensures conformance to this Standard.

1.3 Purpose

Excipients impact the appearance, stability, and delivery of drug products and are essential to the safety, quality, and efficacy of these products. Testing of excipients cannot ensure detection of the myriad of possible contaminants and functional deficiencies from poor excipient manufacturing practices that may result in a finished drug product that is ineffective or adversely affects patient health.

2 Reference documents

2.1 Normative references

WHO, Guidelines for Drinking-Water Quality, 3rd edition, 2008¹

2.2 Informational references

The following documents were used in the creation of this Standard and provide detailed technical information:

- a) European Commission, EU Guide to Good Manufacturing Practice (GMP): Annex 18 Good Manufacturing Practice for Active Pharmaceutical Ingredients, July 2001²
- b) FDA, Guidance for Industry, Q10 Pharmaceutical Quality System, April 2009³
- c) ICH Harmonised Tripartite Guideline, Q6A: Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances, November 1999⁴
- d) ICH Harmonised Tripartite Guideline, Q8: Pharmaceutical Development, November 2005⁴
- e) ICH Harmonised Tripartite Guideline, Q9: Quality Risk Management, November 2005⁴
- f) ISO 9001:2008, Quality management systems – Requirements, October 2008⁵
- g) International Pharmaceutical Excipients Council, IPEC Americas® Certificate of Analysis Guide for Bulk Pharmaceutical Excipients, 2000⁶
- h) International Pharmaceutical Excipients Council, Joint IPEC – PQG Good Manufacturing Practices Guide for Pharmaceutical Excipients, 2006⁶
- i) The United States Pharmacopeial Convention, United States Pharmacopeia-National Formulary, Second Supplement to the USP 33–NF 28 Reissue, 2011⁷

3 Definitions

Terms used in this Standard, which have a specific technical meaning, are defined here.

- 3.1 **active pharmaceutical ingredient (API):** Any substance or mixture of substances 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 pharma-

¹ World Health Organization, Avenue Appia 20, 1211 Geneva 27, Switzerland <www.who.int>.

² European Commission, DG Health and Consumer Protection, B-1049 Brussels, Belgium <ec.europa.eu>.

³ Food and Drug Administration, 10903 New Hampshire Ave., Silver Spring, MD 20993-0002, USA <www.fda.gov>.

⁴ International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), 15, chemin Louis-Dunant, P.O. Box 195, 1211 Geneva 20, Switzerland <www.ich.org>.

⁵ International Organization for Standardization (ISO), 1, ch. de la Voie-Creuse, Case postale 56, CH-1211 Geneva 20, Switzerland <www.iso.org>.

⁶ International Pharmaceutical Excipients Council of the Americas, 1655 North Fort Myer Drive, Suite 700 Arlington, VA 22209, USA <www.ipecamericas.org>.

⁷ The United States Pharmacopeial Convention, 12601 Twinbrook Parkway, Rockville, Maryland 20852–1790, USA <www.usp.org>.

- cological 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 man or animals.
- 3.2 **adequate:** Sufficient, although not necessarily the most or the best.
- 3.3 **appropriate:** A quality of being just right for the requirements.
- 3.4 **archival system:** System used to preserve information considered valuable, using media suitable for storage and retrieval.
- 3.5 **batch:** A specific quantity of material produced in a process or a series of processes so that it may be expected to be homogenous. In the case of a continuous process, a batch may correspond to a defined fraction of the production. The batch size may be defined by a fixed quantity or by the amount produced in a fixed time interval.
- 3.6 **calibration:** The demonstration that a particular instrument or measuring device produces results within specified limits by comparison with results produced by using a reference or traceable standard, over an appropriate range of measurements.
- 3.7 **certificate of analysis (COA):** A document listing the test methods, specifications, and results of testing a representative sample from the batch to be delivered.
- 3.8 **certificate of conformity (COC):** A document that confirms the product shipped to the customer complies with a specific set of requirements or specifications. It does not contain actual test results.
- 3.9 **change control:** A process used for management review of proposed changes that may impact the quality or regulatory conformance of the excipient.
- 3.10 **competency:** The demonstrated personal attributes and ability to apply knowledge and skills.
- 3.11 **component:** Any material present in the excipient that arises as a consequence of the raw materials and/or manufacturing process.
- 3.12 **computer system:** A group of hardware components and associated software designed and assembled to perform a specific function or group of functions.
- 3.13 **contaminant:** An undesired material of a chemical or microbiological nature, or foreign matter introduced from a raw material, intermediate, or excipient during production, sampling, packaging, storage or transport.
- 3.14 **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.
- 3.15 **continual improvement:** Recurring activity to increase the ability to fulfill requirements.
- 3.16 **continuous process:** A process that continually produces material from a continuing supply of raw material.
- 3.17 **corrective action:** The action taken to eliminate the cause of a detected non-conformity or other undesirable situation. NOTE – Corrective action is taken to prevent recurrence whereas preventive action is taken to prevent occurrence.

- 3.18 **critical:** A process step, process condition, test requirement, or other relevant parameter or item that must be controlled within predetermined criteria to ensure that the excipient meets its specifications.
- 3.19 **customer:** The organization receiving the excipient once it has left the control of the excipient manufacturer; includes brokers, agents and users.
- 3.20 **documented procedure:** A written procedure meeting the requirements of 4.2.3.
- 3.21 **drug product:** Dosage form intended for use by a patient.
- 3.22 **effectiveness:** An expression of the degree to which activities have produced the effects planned.
- 3.23 **excipient:** Substances other than the API that have been appropriately evaluated for safety and are intentionally included in a drug delivery system.
- 3.24 **excipient realization:** Achievement of an excipient with the quality attributes appropriate to meet the needs of internal customers, pharmaceutical users, regulatory authorities, health care professionals, and patients.
- 3.25 **expiry (expiration) date:** The date designating the time before which the excipient is expected to remain within specifications and after which it must not be used.
- 3.26 **functionality:** A desirable property of an excipient that aids and/or improves the manufacture, quality, or performance of the drug product.
- 3.27 **good manufacturing practices (GMP):** Requirements for the quality system under which drug products and their ingredients are manufactured. Current Good Manufacturing Practices (cGMP) is the applicable term in the United States. For the purposes of this Standard, the terms GMP and cGMP are equivalent.
- 3.28 **ICH:** International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.
- 3.29 **IPEC:** International Pharmaceutical Excipients Council.
- 3.30 **IPEC-PQG:** International Pharmaceutical Excipients Council and the Pharmaceutical Quality Group.
- 3.31 **impurity:** A component of an excipient that is not intended to be present but arises as a consequence of the production process.
- 3.32 **justified:** A documented explanation.
- 3.33 **lot:** (see “batch”)
- 3.34 **mother liquor:** The residual liquid that remains after crystallization or isolation processes.
- 3.35 **nonconformance:** A non-fulfillment of a requirement.
- 3.36 **packaging material:** A material intended to protect an intermediate or excipient during storage and transport.

- 3.37 **preventive action:** The action taken to eliminate the cause of a potential non-conformity or other undesirable potential situation. NOTE – Preventive action is taken to prevent occurrence whereas corrective action is taken to prevent recurrence.
- 3.38 **primary reference standard:** A substance that has been shown by an extensive set of analytical tests to be authentic material that is of high purity. This standard may be: (1) obtained from an officially recognized source, or (2) prepared by independent synthesis, or (3) obtained from existing production material of high purity, or (4) prepared by further purification of existing production material.
- 3.39 **process:** The combination of operating steps including synthesis, isolation, purification, packaging, etc. that produces the finished excipient.
- 3.40 **product lifecycle:** All phases in the life of the product from the initial development through marketing until the product's discontinuation.
- 3.41 **production:** Operations involved in the preparation of an excipient from receipt of materials operations through processing and packaging to the finished excipient.
- 3.42 **quality:** The suitability of an excipient for its intended use. This term includes such attributes as the identity, strength, and purity.
- 3.43 **quality control (QC):** Checking or testing that specifications are met.
- 3.44 **quality-critical:** 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.
- 3.45 **quality management system (QMS):** A management system that directs and controls an organization with regard to quality.
- 3.46 **quality risk management:** A systematic process for the assessment, control, communication, and review of risks to the quality of the excipient across its lifecycle.
- 3.47 **quality system:** The sum of all aspects of a system that implements quality policy and ensures that quality objectives are met.
- 3.48 **quality unit:** An organizational unit independent of the production unit that fulfills both Quality Assurance (QA) and Quality Control (QC) responsibilities. This may be in the form of separate QA and QC units, a single individual, or a single group, depending upon the size and structure of the organization.
- 3.49 **quarantine:** The status of materials isolated physically or by other effective means pending a decision on their subsequent approval or rejection.
- 3.50 **raw material:** A general term used to denote starting materials, reagents, and solvents intended for use in the production of intermediates or excipients.
- 3.51 **record:** A document stating results achieved and/or providing evidence of activities performed. The medium may be paper, magnetic, electronic or optical, photographic, etc. or a combination thereof.
- 3.52 **representative sample:** Sample obtained according to a sampling procedure designed to ensure that the different parts of a batch or the different properties of a non-uniform material are proportionately represented.

- 3.53 **reprocessing:** Repetition of an activity that is a normal part of the manufacturing process and that has been documented previously.
- 3.54 **requirements:** The explicit or implicit needs or expectations of the governing standards.
- 3.55 **retained sample:** A representative sample of a batch/delivery that is of sufficient quantity to perform at least two full quality control analyses and will be kept for a defined period of time.
- 3.56 **retest date:** The date when a material must be re-examined to ensure that it is still suitable for use.
- 3.57 **retest/re-evaluation interval:** The duration, normally expressed in months or years, from the date of manufacture, throughout which the excipient is expected to continue to conform to the specifications and after which must be tested to confirm it continues to meet the specifications.
- 3.58 **retest interval:** (see “retest/re-evaluation interval”)
- 3.59 **reworking:** Subjecting previously processed material that did not conform to standards or specifications to processing steps that differ from the normal process.
- 3.60 **risk analysis:** The estimation of the risk(s) associated with the identified hazard(s).
- 3.61 **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.
- 3.62 **secondary reference standard:** A substance of established quality and purity, as shown by comparison to a primary reference standard, used as a reference standard for routine laboratory analysis.
- 3.63 **shelf life:** The length of time during which the excipient meets specifications (see 3.25 “expiry (expiration) date,” 3.59 “retest/re-evaluation interval,” and 3.60 “retest interval”).
- 3.64 **significant change:** Any change that alters an excipient’s physical or chemical property from the norm, or that is likely to alter the excipient’s performance in the dosage form.
- 3.65 **solvent:** An inorganic or organic liquid used as a vehicle for the presentation of solutions or suspensions in the manufacture of an excipient.
- 3.66 **specification:** A test or list of tests, references to analytical procedures and appropriate acceptance criteria that are numerical limits, ranges or other criteria, that a material is required to meet.
- 3.67 **specificity:** The ability to assess unequivocally the analyte in the presence of components that may be expected to be present. Typically these might include impurities, degradants, matrix, etc.
- 3.68 **stability:** The continued conformance of the excipient to its specifications.
- 3.69 **state of control:** A condition in which the set of controls consistently provides assurance of continued process performance and product quality.
- 3.70 **subcontractor:** A third party for outsourced work or services that contribute in whole or in part to the manufacture of excipients.
- 3.71 **top management:** A person or group of people who direct and control an organization at the highest level. The highest level may either be at the site or corporate level and will depend on how the quality management system is organized.

- 3.72 **traceability:** The ability to determine the history, application, or location that is under consideration (for example, origin of materials and parts, processing history, or distribution of the product after delivery).
- 3.73 **validation:** A documented program that provides a high degree of assurance that a specific product, method, procedure (e.g., cleaning), or system will consistently produce a result meeting predetermined acceptance criteria.
- 3.74 **verification:** The application of methods, procedures, tests, and other evaluations, in addition to monitoring, to determine compliance with GMP principles.

4 Quality Management System

4.1 General Requirements

The organization shall document, manage, and implement the quality management processes and GMP required to assure excipient quality.

NOTE 1 – The elements of the quality management processes should be applied in a manner that is appropriate and proportionate to each of the product lifecycle stages, recognizing the different goals and knowledge available at each stage.

The organization shall maintain and continually improve the quality management system and GMP in accordance with the requirements of this Standard.

4.1.1 General Quality Management Process Organization

In defining the quality management processes the organization shall:

- a) define individual and collective roles, responsibilities, authorities and inter-relationships of all organizational units related to the excipient quality management system; ensure these interactions are communicated and understood at all relevant levels of the organization,

NOTE 2 – An independent quality unit with authority to fulfill certain excipient quality system responsibilities is required by regional regulations.

- b) define the interactions of the processes stated herein, with the operations needed for the quality management system and the implementation of GMP,
- c) determine the criteria and methods to ensure that the operation and control of these processes and GMP are effective,
- d) ensure that there are suitable resources, including availability of information, to support the operation and measurement of these processes,
- e) monitor, and, where applicable, measure and analyze these processes and procedures to gain knowledge and understanding of them, and

NOTE 3 – Processes here include the quality management system and the manufacturing and delivery operations.

- f) apply actions based on the science and knowledge gained to improve these processes and the quality management system while maintaining consistent excipient quality.

NOTE 4 – Quality risk management may be useful for identifying and prioritizing areas for continual improvement.

4.1.2 Outsourcing General Requirements

Where manufacturing, testing, or other operations that may affect excipient quality are outsourced, the organization shall:

- a) define the responsibility for quality and the control measures within the quality management system (see 7.4), and
- b) demonstrate that the applicable GMP principles in accordance with this Standard are applied to those operations.

The organization shall define and document the point in the manufacture and supply of the excipient at which the full requirements of this Standard apply.

4.2 Documentation Requirements

4.2.1 General

The design, organization, and documentation of the quality system shall be structured to facilitate common understanding and consistent application.

The use of appropriate quality risk management principles shall be incorporated into the design of the quality management system.

NOTE 1 – Quality risk management may be a useful aid to identifying activities, operations, and processes that pose a risk to consistent excipient quality.

The following documents shall be included in the quality management system:

- a) Quality Manual, (see 4.2.2),
- b) Quality Objectives, and
- c) documents and records required by this Standard.

NOTE 2 – A single document may address the requirements of one or more procedures. More than one document may be used to meet the requirement for a documented procedure.

NOTE 3 – The extent of the documentation system will vary from organization-to-organization and depend on the size and range of activities in the organization, the number of employees and excipients supplied, and the competency of the personnel.

NOTE 4 – The documentation may be in any form or type suitable for long-term storage and retrieval.

4.2.2 Quality Manual

The organization shall prepare a Quality Manual describing the quality management system, the Quality Policy, and the commitment of the organization to apply the GMP and quality management requirements contained in this Standard. The Quality Manual shall also include:

- a) the scope of the quality management system,
- b) reference(s) to supporting procedures,

- c) a description of the interaction between quality management processes, and
- d) identification of the point at which GMP as described herein is applied to the organization's manufacturing operations.

4.2.3 Control of Documents

Documents required by this Standard and those determined by the organization as necessary to implement GMP and the quality management system shall be controlled. Records are a special type of document and shall be controlled according to the requirements specified in 4.2.4.

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

- a) approve documents for adequacy by designated personnel prior to issue,
- b) periodically review, update as necessary, and re-approve documents,
- c) ensure that changes and the current revision status of documents are identified,
- d) ensure that current versions of applicable documents are available at points of use,
- e) ensure that documents remain legible and readily identifiable,
- f) ensure that documents of external origin are identified and their distribution controlled, and
- g) prevent the unintended use of obsolete documents and to apply suitable identification to them if they are retained for any purpose.

Documents that impact excipient quality shall have a defined owner and be reviewed and approved by the quality unit before issue (see 5.5.1).

Electronic documentation shall meet the requirements for the document control system stated above. If electronic signatures are used on documents they shall be controlled to provide equivalent security to those given by a hand written signature.

NOTE – Electronic documents and signatures may also need to satisfy local regulatory requirements.

4.2.4 Control of Records

The organization shall establish and maintain a documented procedure for the identification, collection, indexing, filing, storage, maintenance, protection, retention time, and disposition of records.

Records shall be established and maintained to demonstrate achievement of the defined specifications and conformance with this Standard. Records shall be legible and stored in such a manner that they are readily retrievable. Electronic records shall be subjected to the same controls as those required for other records. Pertinent subcontractor quality data shall be an element of these records.

Entries in records shall 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 shall be signed and dated, leaving the original entry legible.

The record retention period shall not be less than three years past the excipient's expiry or first re-evaluation date.

NOTE – The minimum record retention period is set to consider the typical shelf life of a drug product.

4.3 Change Control

Top management shall ensure the integrity of the quality management system is maintained when changes are planned and implemented.

There shall be a documented procedure for the evaluation and approval of changes that may impact upon the quality of the excipient, including the impact on any regulatory submissions by the excipient manufacturer. The evaluation and approval of planned changes shall occur prior to the implementation of the changes. (For requirements regarding the evaluation and approval of unplanned changes, see 8.5.2.) A unit independent from production shall approve changes that may impact the quality of the excipient. Where impact on the quality of the excipient is potentially significant, the change shall be communicated to customers (see 7.2.3) and, as applicable, regulatory authorities.

NOTE – Quality risk management may be utilized to evaluate proposed changes. The level of effort of the evaluation should be commensurate with the level of risk but the evaluation shall always be documented.

5 Management Responsibility

5.1 Management Commitment

5.1.1 Top management shall have the responsibility to:

- a) ensure an effective excipient quality management system is in place to achieve the Quality Objectives and that roles, responsibilities, and authorities are defined, communicated, and implemented,
- b) communicate to the organization the importance of conforming to the Quality Policy and support achievement of the Quality Objectives,
- c) provide evidence of its commitment to meeting the requirements of this Standard, the relevant statutory and regulatory requirements, and customer expectations, and
- d) ensure a timely and effective communication and escalation process exists to raise quality-critical issues of conformance to this Standard or regulatory requirements to top management.

5.2 Customer Focus

It is the responsibility of top management to ensure customer key requirements are identified, established and met.

NOTE – Customer key requirements as they relate to this Standard 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.

5.3 Quality Policy

Top management shall establish a quality policy that describes the overall intentions and direction of the organization related to quality. The Quality Policy shall:

- a) include commitments to implementation of GMP, compliance with applicable regulatory requirements, and continual improvement,

- b) be communicated to and understood by personnel at all levels in the organization, and
- c) be reviewed at a defined frequency for continuing suitability (see 5.6).

5.4 Planning

5.4.1 Quality Objectives

Top management shall ensure Quality Objectives are established for relevant functions and levels within the organization for adherence to this Standard. The organization shall maintain, regularly review, and demonstrate its performance against Quality Objectives. Quality Objectives shall be deployed throughout the organization and shall be understood, measurable, and consistent with the Quality Policy.

5.4.2 Quality Management System Planning

Top management shall provide adequate resources to ensure conformance to the provisions of this Standard. There shall be a process for the identification of resources needed for adherence to this Standard.

NOTE – A gap analysis based on audits by internal personnel, customers, regulatory agencies, or outside contractors to this Standard may be used for the purpose of identifying resource requirements.

5.5 Responsibility, Authority, and Communication

5.5.1 Responsibility and Authority

Responsibility and authority shall be clearly defined by top management, documented, and communicated within the organization.

The organization shall demonstrate through their organizational structure that the units responsible for the following activities, referred to herein as the quality unit, shall be independent from production. The quality unit shall be responsible for:

- a) approving suppliers of quality-critical materials, components, and services,
- b) approving or rejecting quality-critical materials and components,
- c) ensuring a review of production records is performed to verify no errors have occurred or, if errors have occurred, that they are fully investigated and documented,
- d) reviewing and authorizing changes to processes, specifications, procedures, and test methods that may affect excipient quality (see 4.3),
- e) approving the results of investigations into deviations from process instructions, test or measurement failures, and complaints,
- f) retaining responsibility for approval or rejection of the excipient if it is produced, processed, packaged, or held under contract by another organization, and
- g) implementing an internal audit program of the quality management system (see 8.2.2).

The quality unit may delegate some of the activities listed above when justified as appropriate; however, they shall retain responsibility for oversight of delegated activities and applicable controls.

An organization chart by function shall show inter-departmental relationships as well as relationships to top management of the organization. Personnel who have a direct or significant impact on excipient quality shall have job descriptions and defined responsibility and authority.

5.5.2 Management Representative

A member of the organization's management with sufficient authority shall be appointed to ensure the provisions of this Standard are properly implemented. The representative shall be responsible for the following:

- a) ensuring processes needed for the excipient quality management system are established, implemented, and maintained,
- c) reporting to top management on the performance of the excipient quality management system and any need for improvement, and,
- c) ensuring the promotion of awareness of customer and regulatory requirements throughout the organization, as relevant.

5.5.3 Internal Communication

The organization shall ensure appropriate systems are established to communicate throughout the organization the requirements of this Standard and applicable regulatory requirements. The communication shall also provide information about the effectiveness of the excipient quality management system.

Top management shall be notified in a timely manner of quality-critical situations in accordance with a documented procedure.

5.6 Management Review

5.6.1 General

Top management shall hold scheduled reviews of the excipient quality management system to confirm continued conformance to this Standard. The review shall be documented. Any opportunities for improvement shall be assessed and implemented via the change control procedure (see 4.3).

NOTE – For excipient quality review requirements, see 8.2.3.

5.6.2 Review Input

The management review inputs shall include, at a minimum, performance metrics and trends for:

- a) action items from the previous management review,
- b) results of internal and external audits,
- c) excipient conformity and process performance,
- d) customer feedback regarding the organization's performance,
- e) customer complaints,
- f) status and review of corrective and preventive actions,
- g) changes to the excipient quality management system, and

- h) new, revised, and proposed regulatory requirements.

5.6.3 Review Output

The management review shall identify the resources needed and opportunities presented for improvement of the quality management system and improvement of excipient conformance to customer and regulatory requirements. A record shall be made of all actions ordered and taken.

6 Resource Management

6.1 Provision of Resources

The organization shall provide sufficient resources and qualified personnel to implement and continually improve the excipient quality management system and to manufacture, package, test, store, and release each excipient batch in a manner consistent with this Standard.

6.2 Human Resources

6.2.1 General

Personnel performing work with the potential to affect the quality of excipients shall 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 shall have sufficient education, training, and experience or any combination thereof to advise on the subject for which they are retained. The organization shall maintain records listing the name, address, and qualifications of consultants and the type of service they provide.

6.2.2 Competence, Awareness, and Training

The organization shall identify, establish, and document the training needs for personnel performing activities having the potential to affect excipient quality or elements of this Standard. These employees shall be adequately trained prior to carrying out their assigned duties. Training shall include, at a minimum:

- a) the particular operations the employee performs,
- b) the elements of this Standard as they relate to the employee's duties,
- c) the elements of hygienic practices for personnel whose activities or responsibilities have the potential to result in contamination of the excipient, and
- d) the impact deviations from procedures may have on excipient quality.

The training shall be delivered by qualified individuals at sufficient frequency to ensure employees remain familiar with applicable elements of this Standard. The organization shall maintain records of training, including content, attendance, and trainer qualifications.

6.2.3 Hygienic Practices

To protect excipients from contamination, the organization shall conduct a risk assessment to identify areas where the excipient is at risk for contamination from personnel and/or their activities. As part of the risk assessment and to determine the necessary controls, the organization shall consider the following and any other identified factors:

- a) the personnel themselves and their attire,

- b) the equipment used by the personnel,
- c) the opportunity for loose items to fall into the excipient,
- d) the access of unauthorized personnel to designated areas,
- e) the potential impact of any person with an apparent illness or open lesions, and
- f) the storage and use of food, drink, personal medication, tobacco products, or similar items.

Where existing controls to minimize the risks of excipient contamination are not considered effective then additional measures shall be documented and implemented. The effectiveness of these measures shall be demonstrated and documented.

Personnel shall be instructed to report to supervisory personnel any health conditions that may have an adverse effect on excipients.

6.3 Infrastructure

The infrastructure shall be operated, cleaned, and maintained in accordance with this Standard to ensure excipient quality. There shall be adequate facilities for the relevant activities conducted at the site.

6.3.1 Buildings and Facilities

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

The organization shall conduct a risk assessment based on the organization's purported use to identify areas in which the excipient is at risk for contamination from deficiencies in buildings and/or facilities. The risk assessment shall consider the following, at a minimum, to identify where the excipient is at risk from contamination:

- a) state of repair of the building and facility,
- b) suitable size, construction, and location,
- c) ability to maintain a suitably clean building and facility environment,
- d) operations inside or outside of the building or facility that may affect the excipient quality, and
- e) presence of airborne contaminants, especially highly sensitizing or toxic substances.

Suitable control measures shall be implemented to mitigate the identified risks. The effectiveness of these measures shall be demonstrated and documented.

6.3.2 Equipment

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

- a) maintained in a good state of repair,
- b) of suitable size, construction, and location to facilitate cleaning, maintenance, and correct operation, commensurate with the type of processing, and
- c) constructed so contact surfaces will not be reactive, additive, or absorptive.

Design deficiencies that may impact excipient quality shall be addressed with mitigation strategies.

Where equipment is located outdoors there shall be suitable control to minimize the risk to excipient quality from the environment, including seasonal variations.

6.3.2.1 Equipment Construction

New installations or replacement equipment shall be designed to minimize the possibility of contamination and shall undergo planned activity before use to ensure it is functioning as intended.

The risk of contamination from lubricants, heat transfer fluids, or other media used for proper equipment operation coming into contact with raw materials, packaging materials, intermediates, or finished excipients shall be identified. Where contact from these materials is possible, the substances used shall be justified based on patient safety.

6.3.2.2 Equipment Maintenance

The organization's procedures and associated schedules for equipment maintenance shall be established for the maintenance of quality-critical equipment used in the production, processing, packaging, testing, and holding of the excipient.

There shall be records of the use, maintenance, and associated cleaning of quality-critical equipment.

6.3.2.3 Computer Systems

The organization shall document the following for computer systems that impact excipient quality:

- a) proper operation of the system,
- b) prevention of unauthorized access,
- c) records that demonstrate the computer systems are performing as intended,
- d) disaster recovery procedures, including retention of suitable back-up or archival systems, and
- e) maintenance and assurance that changes are verified and documented and only made by authorized personnel.

6.3.3 Utilities

The organization shall conduct a risk assessment considering the risk to excipient quality from utilities (nitrogen, compressed air, steam, etc.) used in the production, storage, or transfer of materials. Appropriate action shall be taken to control the risk to excipient quality.

6.3.4 Water

Water coming into direct contact with the excipient, intermediate, or excipient contact surfaces shall have documented specifications. Unless otherwise justified, water shall, at a minimum, meet the WHO Guidelines for Drinking-Water Quality.

Where water used in the process is treated by the organization to achieve a defined quality, the treatment process shall be specified and the quality of the water monitored and controlled within specified limits.

If interruptions in the quality of water or supply occur, adequate evidence and appropriate rationale shall be documented to show such interruptions have not compromised the quality of the excipient.

Water that comes into contact with the excipient shall be supplied under continuous positive pressure (or other means of preventing back flow) in a system free of defects to control the risk to the excipient quality.

6.4 Work Environment

The organization shall conduct a risk assessment based on intended route of administration of the dosage form to identify areas in which the excipient is at risk for contamination from exposure to the work environment. Controls shall be applied to maintain a suitable environment to minimize the risk to excipient quality.

The work environment shall be managed and controlled to minimize risks of excipient contamination. A documented risk assessment shall be carried out to determine the necessary controls.

The documented risk assessment shall consider the following controls, as applicable:

- a) air handling systems,
- b) special environments,
- c) cleanliness and sanitary conditions,
- d) waste segregation and disposal,
- e) pest control, and
- f) personnel hygiene.

Where maintenance of the work environment is critical to excipient quality, the controls shall be documented.

6.4.1 Air Handling

Where the risk assessment has identified that an air handling system poses a potential risk to excipient quality, the air handling system shall be designed and maintained to assure adequate protection of the excipient. The organization shall demonstrate its effectiveness.

6.4.2 Controlled Environment

Where the risk assessment has identified the need for a controlled environment, it shall be monitored to assure excipient quality.

Where an inert atmosphere is required, the gas shall be treated as a quality-critical raw material (see 7.4.3).

If interruptions in the controlled environment occur, the organization shall perform an investigation to document adequate evidence and appropriate rationale to show such interruptions have not compromised the quality of the excipient.

6.4.3 Cleaning and Sanitary Conditions

Where the risk assessment (see 6.3.1) has identified that clean and/or sanitary conditions of the work environment are necessary to protect excipient quality, the organization shall document procedures assigning responsibility for cleaning and/or sanitation. Cleaning and/or sanitization records shall be maintained.

Waste shall be segregated and disposed of in a timely and appropriate manner. If waste is not disposed of immediately, it shall be suitably identified.

6.4.4 Pest Control

Where the risk assessment (see 6.3.1) has identified the need for pest control, the organization shall document the pest control program.

6.4.5 Lighting

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

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

6.4.6 Drainage

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

6.4.7 Washing and Toilet Facilities

Personal washing facilities shall be provided, including hot and cold water, soap or detergent, and air dryers or single service towels. Clean toilet facilities shall be separate from but easily accessible to working areas.

Facilities for showering and/or changing clothes shall be provided, where required.

7 Excipient Realization

7.1 Planning of Excipient Realization

The organization shall plan and develop the processes and controls needed for excipient manufacture, including implementation of identified actions from risk assessments described in other sections of this Standard. These plans and controls shall be appropriate to the production process, including subcontractor activities, and include:

- a) equipment and facilities for storage and testing used in the manufacture and supply of the excipient,
- b) testing programs for quality-critical materials and the finished excipient that include appropriate specifications, sampling plans, and test and release procedures, and
- c) environmental and hygiene control programs to minimize contamination of the excipient.

The record system shall demonstrate these processes and controls were followed.

The use of recycled or recovered materials containing recoverable amounts of excipient, reactants, or intermediates shall be justified.

7.2 Customer-Related Processes

7.2.1 Determination of Requirements Related to the Product

The organization shall determine the excipient quality, labeling, legal, and regulatory requirements, as well as those provided by the customer. Requirements not stated by the customer but necessary for the specified or intended use, where known, shall be considered. Changes requiring notification and/or documented prior approval from the customer shall be determined.

7.2.2 Review of Requirements Related to the Product

The organization shall review the requirements identified in 7.2.1 to assure the facilities and processes are capable of consistently meeting these requirements and shall document the review and agreement with the customer before supply commences. Where the requirements determined in 7.2.1 are changed, this review shall be repeated before supply recommences.

7.2.3 Customer Communication

The organization shall provide accurate and pertinent communication to the customer. The organization shall determine the types of excipient quality-related documents shared with customers and which shall be controlled. At a minimum, master copies of quality-related documents made available to customers shall be controlled within the organization. Provision shall be made for replying to customer enquiries, contracts, and order handling requirements. Customer feedback and complaints shall be documented.

The organization shall define how potentially significant changes are assessed (see 7.2.2) and communicated to customers (see 4.3).

7.3 Design and Development

The organization shall establish which provisions of this Standard shall be applicable for the design and development of excipients. The organization shall manufacture development batches of excipients intended for use in human or veterinary subjects in accordance with this Standard. The organization shall communicate to the customer(s) the extent to which the excipient was manufactured to this Standard.

NOTE – ISO 9001 includes requirements for ensuring control over design and development activities. Companies involved in such activities are recommended to follow the requirements of ISO 9001.

7.4 Purchasing

7.4.1 Purchasing Process

The organization shall establish a system for selecting, approving, and reapproving suppliers of materials and services. Quality-critical materials and services shall be identified from risk assessments.

Supplier approval of quality-critical materials and services shall require a documented evaluation by the organization's quality unit of the supplier's quality management system, including adequate evidence, through monitoring and review of the supplier performance, that they are consistently meeting agreed requirements. The organization's quality unit shall approve suppliers of quality-critical materials and services. The organization's quality unit shall also document periodic performance evaluations of supplier quality history including the supplier's ability to consistently meet agreed requirements and the supplier's quality management system.

Materials shall be purchased against an agreed specification from approved suppliers. For quality-critical materials and services, the supplier shall have an agreement to notify the organization of significant changes.

The organization shall require that contract service providers adhere to the relevant sections of this Standard.

7.4.2 Purchasing Information

The organization shall communicate purchasing information to approved suppliers. The purchasing information shall describe the material or service ordered including, at a minimum, the following:

- a) reference to the current agreed specifications or description of service requirements, and
- b) drawings, process requirements, inspection instructions, and other relevant technical data, including requirements for approval or qualification of product, procedures, process equipment, and personnel.

There shall be a written agreement between the organization and subcontract manufacturers, laboratories, and service providers that defines responsibilities for adherence to the sections of this Standard applicable to their activities.

7.4.3 Verification of Purchased Product

The organization shall establish procedures describing the verification, approval, and release of all purchased material used for excipient manufacture and packaging. The organization shall justify 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 shall verify the measurements reported on the supplier Certificate of Analysis meet the agreed specifications. For packaging components, the organization shall verify the Certificate of Conformance references the current agreed specifications. Wherever feasible, the organization shall perform at least an identification test or otherwise confirm the identity of the material.

Procedures shall describe the quarantine of purchased materials prior to their approval. Where quarantine of unapproved material is not possible, the organization shall have an agreement with the supplier so they are promptly notified of material that does not meet specifications.

Any sampling activities shall be performed in accordance with a defined sampling method and using procedures designed to prevent contamination and cross-contamination.

The organization shall establish controls to assure materials delivered in bulk or returnable containers are free from contamination.

7.5 Production and Service Provision

7.5.1 Control of Production and Service Provision

The organization shall conduct excipient production activities in accordance with the following:

- a) production instructions that describe the manufacture of the excipient and that establish records providing sufficient detail to ensure the following:
 - i) the excipient was manufactured and packaged according to the production instructions,
 - ii) the time and date of quality-critical activities performed,
 - iii) the identification of individuals performing such activities,
 - iv) the traceability of materials (including recycled and recovered materials), and
 - v) the identification and traceability of equipment used, maintenance, and cleaning,

- b) equipment and utensil cleaning and sanitization procedures justifying the method and frequency of cleaning, establishing criteria for determining effectiveness, and requiring records of cleaning activities as noted above; the cleaning status of equipment shall be known,
- c) state of process control using documented in-process testing on representative samples obtained using prescribed sampling protocols or plans, or through in-line testing and
- d) packaging and labeling control procedures that ensure labels are printed and issued containing the correct information are applied to all containers, and that unused coded labels and unneeded packaging materials are immediately removed from the area.

Where solvents are recovered for reuse, they shall meet appropriate specifications prior to reuse or mixing with other approved solvent.

7.5.2 Validation of Processes for Production and Service Provision

The organization's excipient quality management system shall provide ongoing evidence that the processes are capable of consistently achieving the desired quality outcome based on knowledge of process parameters, excipient attributes, and their inter-relationship.

NOTE – The validation program typically performed in the pharmaceutical industry may not always be carried out by the excipient manufacturer. However, consistent operation may be demonstrated by, for example, process capability studies, development and scale-up reports, etc.

After significant changes, the impact on validation or process capability shall be assessed.

7.5.3 Identification and Traceability

The organization shall establish a system to identify the quality-critical materials used in the manufacture and packaging of the excipient and their inspection status.

Records shall provide traceability of the excipient and contact packaging throughout excipient realization to delivery to initial customers. Methods used for identification and traceability of raw materials used in excipients produced by continuous processing shall be defined.

The organization shall ensure there is a process to communicate the origin and traceability of the excipient to the customer. Labeling shall meet applicable regulatory requirements, and, at a minimum, labels shall include:

- a) the name of the excipient and, if applicable, grade,
- b) the organization's name and manufacturing address,
- c) the batch number, and
- d) storage conditions, if other than ambient (i.e., uncontrolled temperature and humidity).

7.5.4 Customer Property

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

The organization shall also make provisions to protect other real and intellectual property (e.g., test equipment, test methods, and specifications) provided by the customer.

7.5.5 Preservation of Product

The organization shall define and justify the conditions for the handling and storage of quality-critical materials (see 7.5.3) so their identity, quality, and conformance to specifications are not affected. Records of storage conditions shall be maintained when such conditions are critical to the material's quality characteristics. Deviations from specified storage conditions shall be assessed and documented.

7.5.5.1 Raw Material Packaging Systems

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

- a) provide suitable protection against deterioration and contamination, and
- b) ensure identification labels remain legible.

7.5.5.2 Excipient Packaging Systems

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

- a) documented specifications,
- b) documented evidence that packaging does not adversely impact quality (e.g., packaging is not reactive, additive, or absorptive),
- c) documented cleaning procedures (where containers are reused), and
- d) tamper-evident seals.

Containers shall be stored so as to protect their cleanliness. Where excipient containers are returned and reused, the organization shall establish procedures to ensure all previous labels are removed or completely obliterated. The cleanliness of reused containers shall be verified prior to use.

7.5.5.3 Excipient Delivery

Where contractually specified, protection shall extend to include delivery to the final destination.

Excipients shall only be supplied within their expiry period, or as otherwise contractually agreed or specified. When no expiry period is defined, the excipient shall only be supplied within its retest period as supported by stability data (see 8.2.4.7).

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

- a) excipient name or unique identifier,
- b) excipient batch number,
- c) type of packaging,
- d) where and to whom the excipient was shipped,
- e) quantity shipped, and

- f) the date of shipment.

7.6 Control of Monitoring and Measuring Equipment

For quality-critical measurements, the organization shall use appropriately calibrated or verified measuring and test devices. Such measuring and test devices shall have the appropriate specificity and sensitivity. Records of calibration and verification results shall be maintained.

The organization shall 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 shall include the standardization or calibration of quality-critical measuring and test devices at suitable intervals. This program shall contain specific limits for accuracy and precision, and provisions for remedial action in the event that accuracy and/or precision limits are not met. Calibration and confirmation standards shall be traceable to applicable national, international, or compendial standards. Where no such standards exist, the basis used for calibration or verification shall be justified.

The calibration status of quality-critical equipment shall be identified and accessible to the user of the equipment.

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

8 Measurement, Analysis and Improvement

8.1 General

The organization shall plan and implement the monitoring, measurement, and improvement activities required to demonstrate conformity of the excipient to customer requirements and to ensure conformity of the quality management system to this Standard.

The organization shall evaluate opportunities for improvements through the measurement and analysis of product and process trends.

8.2 Monitoring and Measurement

8.2.1 Customer Satisfaction

The organization shall establish measurement activities to assess the level of customer satisfaction. These activities shall support improvement of customer satisfaction.

NOTE – Such measurements may include investigation of and response to customer complaints, return of excipients, and customer feedback.

This information shall drive activities that strive to continually improve customer satisfaction.

8.2.2 Internal Audit

The organization shall carry out a comprehensive system of planned, scheduled, and documented internal quality audits. Audits shall be conducted by qualified individuals independent of the area being audited according to documented procedures that include, at a minimum, the following:

- a) determination of the effectiveness of quality activities,
- b) compliance with procedures and processes described by the quality management system,

- c) schedules based on past performance and criticality of the activity to the finished excipient quality,
- d) provisions for follow-up actions,
- e) positive findings that support the effective implementation of GMP, and
- f) deficiencies that need corrective and/or preventive action.

Audit results shall be documented and discussed with management personnel having responsibility in the area(s) audited. Management personnel responsible for the area(s) audited shall take corrective action and/or preventive action on each nonconformance found.

8.2.3 Monitoring and Measurement of Processes

The organization shall identify the tests and measurements necessary to adequately control the manufacturing and quality of the excipient.

Where critical to excipient quality, methods used to verify that the processes are in control shall be established and documented.

Regular review of key indicators, including critical process parameters and critical quality attributes, shall be conducted to assess the need for improvements.

8.2.4 Monitoring and Measurement of Product

The organization shall establish and document the test methods and procedures used to verify the excipient meets specifications.

Test methods shall be suitable for their intended purpose.

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

- a) non-compendial analytical tests shall be demonstrated to be at least equivalent to those in the compendia, and
- b) the excipient shall comply with applicable general chapters and notices.

NOTE 1 – The US Federal Food, Drug, and Cosmetic Act recognizes two official compendia: United States Pharmacopoeia (USP) and National Formulary (NF).

NOTE 2 – The USP-NF is legally two separate compendia published in the same book.

NOTE 3 – The General Notices to both the USP and NF apply to all monographs in the respective compendium unless otherwise stated.

NOTE 4 – In the USP-NF General Chapters having a number below <1000> are mandatory. Chapters having a number between <1000> and <1999> are General Information Chapters. However, if a General Information Chapter is referenced in a particular monograph, it becomes mandatory for that monograph. (Chapters with numbers <2000> or greater apply only to nutritional supplements.)

NOTE 5 – Other pharmacopoeias have different ways of presenting such information. The introductory notices to the specific pharmacopoeia should be consulted.

8.2.4.1 Laboratory Controls and Records

8.2.4.1.1 Laboratory Controls

Laboratory controls shall include complete data derived from tests necessary to verify conformance with specifications and standards including:

- a) a description of the sample received for testing together with the material name, batch number or other distinctive code, and date the sample was taken,
- b) documentation of sample preparation in conformance with test requirements,
- c) a statement referencing each test method used,
- d) a 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,
- e) a record of calculations performed in connection with the test,
- f) test results and how they compare with established specifications, and
- g) a record of the person who performed each test and the date(s) the tests were performed.

8.2.4.1.2 Laboratory Procedures

There shall be documented procedures for the following:

- a) laboratory reagents and test solutions prepared in-house shall include a record of their preparation; whether prepared in-house or purchased, labeling shall include name, concentration, date of first use, and, where assigned, the expiration date,
- b) provisions for the receipt, storage, and use of primary reference standards, and
- c) preparation, identification, testing, approval, and storage of secondary reference standards, including qualification and the requalification period against the primary reference standard.

8.2.4.2 Finished Excipient Testing and Release

Appropriate measures for verification of excipient quality shall be performed to confirm that the excipient conforms to documented specifications. Records shall confirm excipients produced by continuous processes conform to specifications as shown through the results of in-process testing, other process control records, finished package testing, etc.

There shall be a procedure to ensure the quality unit has evaluated the appropriate manufacturing and test documentation prior to quality unit release of the finished excipient.

8.2.4.3 Out-of-Specification Test Results

Out-of-specification (OOS) test results shall be investigated and recorded according to a documented procedure.

Where there is no assignable cause to invalidate the original results/data, the OOS procedure shall define the following, at a minimum:

- a) statistical techniques to be used and under what circumstances,

- b) criteria for the use of retest sample results, and
- c) criteria for resampling.

8.2.4.4 Retained Samples

A representative sample of each batch of the excipient shall be retained, unless the hazard or physical characteristics of the excipient preclude retention of a sample. The organization shall justify and document decisions to not retain a sample of an excipient.

The retention period shall be justified and based upon the expiry, maximum retest period, or date received by the final customer.

Retained samples shall be stored in a secured location, readily retrievable, and in conditions consistent with commercial storage conditions.

The sample size shall be at least twice the amount required to perform complete specifications testing.

8.2.4.5 Certificates of Analysis

The organization shall provide Certificates of Analysis to the required specifications for each batch of excipient.

The Certificate of Analysis shall include, at a minimum:

- a) excipient name and, if applicable, grade and compendial reference,
- b) manufacturer's name and site of manufacture,
- c) date of manufacture,
- d) batch number,
- e) expiration or retest date,
- f) statement of compliance to the required specifications,
- g) statement of compliance to GMP as defined by this Standard,
- h) analytical results specific to the batch, unless otherwise noted and explained,
- i) acceptance criteria,
- j) analytical method reference, and
- k) name and title of person authorizing the Certificate of Analysis.

NOTE – See guidance as provided by the *IPEC Americas® Certificate of Analysis Guide for Bulk Pharmaceutical Excipients*.

8.2.4.6 Excipient Composition

The organization shall identify, where possible, and set limits for excipient composition, including known impurities.

The limits shall be based upon appropriate safety data, limits as described in official compendia or other requirements, and sound GMP considerations.

Manufacturing processes shall be adequately controlled so the excipient composition falls within established limits.

For excipients extracted from or purified using organic solvents, excipient specifications shall include tests and limits for organic solvent residues.

8.2.4.7 Stability and Expiry/Retest Periods

The stability of the excipient shall be documented.

The stated stability of the excipient shall be demonstrated through:

- a) historical data, and/or
- b) on-going stability studies.

An expiry or retest period for the excipient shall be determined, justified, and communicated to the customer.

NOTE – See guidance as provided by the IPEC Excipient Stability Program Guide 2010.

8.3 Control of Nonconforming Product

Raw material, intermediate, and finished excipient not meeting its specifications shall be clearly identified and controlled to prevent inadvertent use or release for sale.

A record of nonconforming product shall be maintained. Incidences of nonconformance shall be investigated to identify the root cause and impact on other batches/products. The investigation shall be documented and action taken to prevent recurrence (see 8.5). The potential impact on validation shall be assessed.

There shall be a documented procedure defining how the retrieval of an excipient from distribution shall be conducted and recorded.

Procedures shall exist for the evaluation and subsequent disposition of nonconforming intermediates and excipients (see 5.5.1).

Nonconforming excipient shall be reviewed in accordance with documented procedures to determine if it may be:

- a) reprocessed/reworked to meet the specified requirements,
- b) accepted by the customer with their agreement,
- c) re-graded for other applications, or
- d) destroyed.

8.3.1 Reprocessing

Reprocessing shall only occur when it has already been documented that the excipient may be made in the same manner. The organization shall maintain records of reprocessing activities in order to ensure traceability of the reprocessed material into the finished excipient.

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

8.3.2 Reworking

Rework involves processing steps that are not routinely performed. Reworking excipient, therefore, is a change under the provisions of change control in this Standard (see 4.3) and shall 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 shall be completed and the following shall be considered, unless otherwise justified:

- a) additional testing to control the reworking,
- b) additional acceptance criteria for the reworked excipient,
- c) impact on stability or the validity of the re-evaluation interval,
- d) performance of the excipient, and
- e) need to notify the customer of reworked excipient.

There shall be records and traceability to the original batches. The equivalence of the quality of reworked material to original material shall also be evaluated and documented to demonstrate the batch will conform to established specifications and characteristics. The evaluation shall be approved by the quality unit.

Batches of excipients that do not conform to specifications individually shall not be blended with batches that do conform, in an attempt to hide adulterated or sub-standard material.

8.3.3 Returned Excipients

There shall be procedures for the evaluation, holding, testing, reprocessing, and reworking of returned excipient.

Returned excipients shall be identified and quarantined until the quality unit has completed an evaluation. When the intent is to make returned excipient available for sale to another pharmaceutical customer, the evaluation shall consider conformance to the required storage and/or transportation conditions throughout the supply chain.

Records for returned excipients shall be maintained and shall 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 shall determine and record the ultimate disposition of returned excipient.

8.4 Analysis of Data

The organization shall define methods for evaluating:

- a) the effectiveness of its quality management system,
- b) the ability to consistently produce conforming excipients,
- c) trending of excipient nonconformance with this Standard, customer complaints, etc., and

- d) trending of supplier nonconformance.

The organization shall use these data to identify opportunities for improvement (see 5.6 and 8.5.1).

8.5 Improvement

8.5.1 Continual Improvement

The organization shall periodically review, including data from 8.4, and improve manufacturing and quality management system processes.

8.5.2 Corrective Action

The organization shall establish procedures for:

- a) determining the root causes of nonconformance,
- b) ensuring corrective actions are implemented and effective, and
- c) implementing and recording changes in procedures resulting from corrective action.

8.5.3 Preventive Action

The organization shall establish procedures for:

- a) initiating preventive actions commensurate with the corresponding risks,
- b) implementing and recording changes in procedures and processes resulting from preventive action, and
- c) ensuring the effectiveness of preventive actions.