MEMORANDUM

TO: Joint Committee on Pharmaceutical Excipients

FROM: Brian Zamora, Chairperson

DATE: June 20, 2019

SUBJECT: Proposed revision to NSF/IPEC/ANSI 363 – *Good Manufacturing Practices for Pharmaceutical Excipients* (363i14r1)

Draft 1 of NSF/IPEC/ANSI 363 issue 14 is being forwarded to the Joint Committee for balloting. Please review the changes proposed to this standard and **submit your ballot by July 11, 2019** via the NSF Online Workspace <www.standards.nsf.org>.

When adding comments please use the provided comment template file in the 'referenced item' section of the ballot and please include the section number applicable your comment and add all comments under one comment number whenever possible.

A 'clean' version of the ballot is also provided in the 'referenced documents' section. Please note that the 'clean' version is there only to help with clarification and is **NOT** part of the ballot. If there is any difference between the documents the ballot document is the official document and whatever is in that document is what is up for ballot. Also, note that while the entire standard is included in this ballot only the grey highlighted and strikethrough portions are being balloted. Comments and negative votes from text not highlighted in grey or with strikethrough will not be addressed in this ballot. Lastly, any formatting issues will be addressed prior to publication and are considered editorial therefore comments on format are not necessary.

Purpose

The purpose of this ballot is to update the standard to be better mapped to the new ISO 9001 format (issue 14). This ballot also closes out issues 11, 12, and 13 which are provided in the referenced item sections as well.

Background

ISO changed the format of 9001 in 2015. This JC made the decision to re-map this standard to that new version in 2016. It has been an ongoing project ever since. This ballot also closes issues 11, 12, and 13. These three issues were discussed and agreed on to go to ballot by the JC but was decided to incorporate them into this ballot so that there was not confusion between drafts.

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If you have any questions about the technical content of the ballot, you may contact me in care of:

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[Note – the recommended changes to the standard which include the current text of the relevant section(s) indicate deletions by use of ~~strikeout~~ and additions by gray highlighting. Rationale statements are in *italics* and only used to add clarity; these statements will NOT be in the finished publication.]

NSF/IPEC/ANSI 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~~1 Scope

This Standard is intended to define Good Manufacturing Practices (GMP) for excipient manufacture and distribution[1] for use in drug products. It sets minimum requirements for GMP applicable to all commercially available excipients.

~~This Standard includes the minimum requirements of a quality management system for excipient manufacture drawing on principles of GMP and quality systems from other relevant standards such as those referenced in section 2.2.~~

[1] GMP applies to distribution per the *Federal Food, Drug, and Cosmetic Act (FD&C Act),* 21 U.S.C. 501(a) (2) (B).

NOTE 1 — The requirements of this Standard may not be sufficient for all applications of excipients. It is the user's responsibility to determine whether or not this Standard meets the requirements for their intended use.

NOTE 2 — Auditing excipient manufacturers ensures conformance to this Standard. This Standard is also intended to be used by duly accredited or otherwise suitably qualified 3rd party audit and certification providers ~~3rd parties~~.

NOTE 3 — Each user of a 3rd party auditing service should make its own determination as to the qualifications of the 3rd party and the applicability of the report and/or certificate issued in satisfying its requirements, including those pertaining to its intended use of the excipient.

1.~~3~~2 Purpose

Excipients impact the appearance, stability, and delivery of drug products and are essential to the safety, quality, and efficacy of these products. It is not possible to assure the consistent quality of excipients by testing alone. Adherence to excipient Good Manufacturing Practices provides assurance that excipients are suitable for use in drug products. Excipient Good Manufacturing Practices require a proper quality management system, test methods, facilities and controls~~, including appropriate tests~~.

2 Reference documents

2.1 Normative references

The following documents contain provisions that, through reference in this text, constitute provisions of this Standard. At the time this Standard was written, the editions indicated were valid. All documents are subject to revision, and parties ~~are encouraged to~~ shall investigate the possibility of applying the most recent edition of the document indicated below. The most recent published edition of the document shall be used for undated references.

WHO, *Guidelines for Drinking-Water Quality*, 4th edition, 2011[2]

2.2 Informational references

The following documents are references that provide supplemental information to the provisions of this Standard. At the time this Standard was written, the editions indicated were valid. All documents are subject to revision, and parties ~~are encouraged to~~ should investigate the possibility of applying the most recent edition of the document indicated below. The most recent published edition of the document shall be used for undated references.

EXCiPACT™, *Certification Standards for Pharmaceutical Excipient Suppliers: Good Manufacturing Practices, Good Distribution Practices*, 2017 ~~2012~~[3]

FDA, *Guidance for Industry: Investigating Out-of-Specification Test Results for Pharmaceutical Production*, October, 2006[4]

FDA, *Guidance for Industry: Q10 Pharmaceutical Quality System*, April 2009[4]

ICH Harmonised Tripartite Guideline, Q6A: *Specifications: Test Procedures and Acceptance Criteria for*

[2] World Health Organization, 1211 Geneva 27, Switzerland <www.who.int/water_sanitation_health/dwq/guidelines/en/index.htm>.

[3] EXCiPACT Association c/o, La Federation du Council International des Excipients Pharmaceutiques (IPEC Federation), Avenue de Gaulois, 9 Brussels B-1040 Belgium < http://www.excipact.org/>.

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

New Drug Substances and New Drug Products: Chemical Substances, November 1999[5]

ICH Harmonised Tripartite Guideline, Q8: *Pharmaceutical Development*, November 2005[5]

ICH Harmonised Tripartite Guideline, Q9: *Quality Risk Management*, November 2005[5]

ISO 9001:20~~08~~15, *Quality management systems – Requirements*, September 2015 ~~October 2008~~[6]

International Pharmaceutical Excipients Council, *IPEC Americas® Certificate of Analysis Guide for Bulk Pharmaceutical Excipients*, 2013[7]

International Pharmaceutical Excipients Council, *IPEC Good Distribution Practices Guide for Pharmaceutical Excipients*, 2017 ~~2006~~[7]

International Pharmaceutical Excipients Council, *IPEC Excipient Stability Program Guide,* 2010[7]

International Pharmaceutical Excipients Council, *Joint IPEC – PQG Good Manufacturing Practices Guide for Pharmaceutical Excipients*, 2017 ~~2006~~[7]

The IPEC-Americas® Significant Change Guide for Bulk Pharmaceutical Excipients, ~~Second~~ Third Revision, March 2017 ~~2009~~[7]

The United States Pharmacopeial Convention, *United States Pharmacopeia-National Formulary (USP 41-NF 36)*, 2018~~2011~~[8]

U.S. Food and Drug Administration, *Federal Food, Drug, and Cosmetic Act* (FD&C Act), 21 U.S.C. 501(a)(2) (B)[9]

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 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 man or animals.

3.2 adequate: Sufficient, although not necessarily the most or the best.

3.3 appropriate: A quality of being suitable for assuring conformance to the requirements.

3.4 archival system: System used to preserve information considered valuable, using media suitable for storage and retrieval.

[5] 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>.

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

[7] International Pharmaceutical Excipients Council of the Americas, 3138 N. 10th Street, Suite 500, Arlington, VA 22201, USA <www.ipecamericas.org>.

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

[9] US Food and Drug Administration, 10903 New Hampshire Ave., Silver Spring, MD 20993-0002 <www.fda.gov>.

3.5 backup: A copy of one or more electronic files created as an alternative in case the original data or system are lost or become unusable and which is maintained securely throughout the record retention period.

NOTE — Backups of electronic records are required because data loss (e.g., through deletion or corruption) during the record retention period is, historically, a common experience compared to paper records.

3.6 batch: A specific quantity of material produced in a process or a series of processes so that it may be expected to be uniform in character and quality, within specified limits. 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.

3.7 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.

3.8 certificate of analysis (COA): A document listing the test methods, specifications, and results of testing a representative sample from the batch to be delivered.

3.9 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.

3.10 change control: A process used for management review of proposed changes that may impact the quality or regulatory conformance of the excipient.

3.11 competency: The demonstrated personal attributes and ability to apply knowledge and skills.

3.12 component: Any material present in the excipient that arises as a consequence of the raw materials and/or manufacturing process.

3.13 computer system: A group of hardware components and associated software designed and assembled to perform a specific function or group of functions.

3.14 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.

3.15 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.

3.16 continual improvement: Recurring activity to increase the ability to fulfill requirements.

3.17 continuous process: A process that continually produces material from a continuing supply of raw material.

3.18 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.

3.19 customer: The organization receiving the excipient once it has left the control of the excipient manufacturer.

3.20 data integrity: The extent to which all data are complete, consistent, reliable and accurate throughout the data lifecycle.

3.21 deviation: Departure from an approved instruction or established standard.

3.22 documented procedure: A written procedure meeting the requirements of 7.5.24~~.2.3~~.

3.23 drug product: Dosage form intended for use by a patient.

3.24 effectiveness: An expression of the degree to which activities have produced the effects planned.

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

3.26 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.

3.27 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.

3.28 functionality: A desirable property of an excipient that aids and/or improves the manufacture, quality, or performance of the drug product.

3.29 good manufacturing practices (GMP): Minimum requirements for the quality management system, methods to be used in, and the facilities or controls to be used for the manufacture, processing, testing, packing, or holding of a drug product and its ingredients. Conformance to these minimum requirements, in part, assures that a drug (i.e., excipient, API, ~~and~~ or drug product~~s~~) will consistently meet quality standards and assure patient safety.

3.30 ICH: International ~~Conference on~~ Council for Harmonisation of Technical Requirements for ~~Registration of~~ Pharmaceuticals for Human Use.

3.31 IPEC: International Pharmaceutical Excipients Council.

3.32 IPEC-PQG: International Pharmaceutical Excipients Council and the Pharmaceutical Quality Group.

3.33 impurity: An undesirable component of an excipient that is present as a consequence of the raw materials, excipient manufacturing process, or excipient degradation. Impurities are expected to be controlled at a specified level.

3.34 justified: A documented explanation.

3.35 label: The display of written, printed or graphic matter on the immediate container of the excipient (inactive ingredient) product.

3.36 labeling: All written, printed or graphic matter accompanying an excipient at any time while it is in-transit to the customer or being held for sale after shipment or delivery to the customer.

3.37 lot: A batch or a specific identified portion of a batch (see “batch”).

3.38 manufacture: Various operations, such as processing, packaging, labeling, and testing.

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

3.40 nonconformance: A non-fulfillment of a requirement.

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

3.42 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.

3.43 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 and to which all like standards are traced and qualified or certified. This standard is preferably obtained from an officially recognized source. If no official recognized source is available, the reference standard selected shall be appropriately characterized.

3.44 process: The combination of operating steps including synthesis, isolation, purification, packaging, etc. that produces the finished excipient.

3.45 product lifecycle: All phases in the life of the product from the initial development through marketing until the product's discontinuation.

3.46 production: Operations involved in the preparation of an excipient from receipt of materials operations through processing and packaging to the finished excipient.

3.47 quality: The suitability of an excipient for its intended use as indicated by relevant physical, chemical, and microbiological properties and as assured by compliance with this Standard.

3.4X quality assurance (QA): The sum total of the organised 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.

3.48 quality control (QC): Checking or testing that specifications are met.

3.49 quality management system (QMS): A management system that directs and controls how the organization implements quality policies and achieves quality objectives.

NOTE — Requirements for quality management systems can be found in *ISO 9001* and *ICH Q10*.

3.50 quality risk management: A systematic process for the assessment, control, communication, and review of risks to the quality of the excipient across its lifecycle.

3.51 quality system: See "quality management system."

3.52 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.

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

3.54 raw material: A general term used to denote starting materials, reagents, and solvents intended

for use in the production of intermediates or excipients.

3.55 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.

3.56 representative sample: A quantity of the excipient taken according to a prescribed rationale so as to accurately portray the material being sampled (e.g., a batch).

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

3.58 requirements: The explicit or implicit needs or expectations of the governing Standards.

3.59 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.

3.60 retest date: The date when a specific batch of material must be re-examined to ensure that it is still suitable for use.

3.61 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.

3.62 retest interval: (see "retest/re-evaluation interval")

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

3.64 risk analysis: The estimation of the risk(s) associated with the identified hazard(s).

3.65 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.

3.66 sanitary: Cleanliness of facility and equipment and maintenance of hygienic conditions which minimize the risk of microbial contamination hazardous to health.

3.67 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.

3.68 shelf life: The length of time during which the excipient meets specifications (see ~~3.24~~3.27 expiry (expiration) date; ~~3.58~~ 3.61 retest/re-evaluation interval; ~~3.59~~ 3.62 retest interval).

3.69 significant change: Any change that has the potential to alter an excipient's physical, chemical, or microbiological property from the norm, and/or that may alter the excipient's performance in the dosage form.

3.70 solvent: An inorganic or organic liquid used as a vehicle for the presentation of solutions or suspensions in the manufacture of an excipient.

3.71 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.

3.72 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.

3.73 stability: The continued conformance of the excipient to its specifications.

3.74 state of control: A condition in which the set of controls consistently provides assurance of continued process performance and product quality.

3.75 subcontractor: A third party for outsourced work or services that contribute in whole or in part to the manufacture of excipients.

3.76 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.

3.77 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).

3.78 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.

3.79 verification: The application of methods, procedures, tests, and other evaluations, in addition to monitoring, to determine compliance with GMP principles.

4 ~~Quality management system~~ Context of the Organization

4.1 ~~General requirements~~ Understanding the organization and its context

The organization shall ensure its quality management system 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 shall be determined and monitored. Internal and external factors shall include the impact of other products produced on the same equipment and outsourced activities (see 8.4) that can affect excipient quality for which the organization has control and responsibility.

The organization shall document and communicate the use for which the excipient is being marketed.

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

~~NOTE — The elements of the quality management 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.~~

4.2 Understanding the needs and expectations of interested parties

The organization shall determine:

- the interested parties that are relevant to the quality management system
- the requirements and expectations of the interested parties shall be determined

The organization shall ensure knowledge of the requirements of the interested parties remains current.

4.3 Determining the scope of the Quality Management System

The organization shall define and document the scope of application of the quality management system to its operations and activities. In determining the scope, the organization shall consider the internal and external factors (see 4.1) and the requirements and expectations of the interested parties (see 4.2) as well as the quality required for the excipient(s). The organization shall determine the appropriate starting point in the manufacture of the excipient where all applicable requirements of this standard apply. Where they are not applicable the organization shall document the reasons.

Conformity to this Standard can only be claimed if the requirements determined as not applicable do not impact the performance of the quality management system or adversely impact the quality of the excipient.

4.4 Quality Management System and Its Processes

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

> NOTE — The elements of the quality management 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**~~**4.4.2** ~~**General quality management systems 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~~ involved with the excipient quality management system~~;~~ and ensure these interactions are communicated and understood at all relevant levels of the organization (see ~~5.5.1~~5.3);

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 — 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 — Quality risk management may be useful for identifying and prioritizing areas for continual improvement.[10]

[10] ICH Harmonised Tripartite Guideline, Q9: *Quality Risk Management*, November 2005

~~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.~~

~~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 changes to the quality management system.~~

~~NOTE — Quality risk management 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 shall be included in the quality management system:~~

~~a) Quality Manual, (see 4.2.2);~~

~~b) Quality Objectives;~~

~~c) documents and records required by this Standard and any other documents necessary for the effective planning, operation and control of the processes; and~~

~~d) a documented risk assessment that defines and justifies when the as/if/where applicable clauses in this Standard are not implemented.~~

~~NOTE 1 — 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 2 — 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) justification of the processing step from which point this Standard shall be applied.~~

~~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.~~

~~Procedures that impact excipient quality shall have a defined owner and be reviewed and approved by the quality unit before issue including changes to these documents (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 that 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 stringency of 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 one year past the excipient's expiry or two years past the retest date. If the manufacturer does not stipulate an expiry or retest/re-evaluation interval, the record retention period shall be a minimum of five years from the date of manufacture. Documented procedures shall be implemented to ensure control of COAs.~~

~~4.3 Change control~~

~~Top management shall establish and maintain a robust change control program under the quality management system. This program shall be designed to ensure that excipient quality is assessed and~~

~~maintained in accord with principles of quality risk management when changes are planned and implemented, respectively.~~

~~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 organization shall define the criteria for a significant change (see 3.69). The evaluation and approval of planned changes shall occur prior to the implementation of the changes. Upon implementation, the effectiveness of a change shall be confirmed. The quality unit shall approve any changes that based on risk assessment may impact the quality of the excipient. There shall be a written procedure for determining which changes to communicate to customers, as well as a mechanism for communicating changes. Significant changes shall be communicated with sufficient notice prior to implementation as is reasonably practical to customers (see 7.2.3) and, as applicable, regulatory authorities. The customer shall be informed prior to the first shipment of the excipient after the change is implemented. Documentation generated for change control shall be retained (see 4.2.4).~~

5 ~~Management responsibility~~ Leadership

5.1 Management commitment

Top management shall have the responsibility to:

a) ensure an effective excipient quality management system is in place to achieve the Quality Objectives;

b) ensure that roles, responsibilities, and authorities are defined, communicated, and implemented;

c) ensure the availability of resources;

d) communicate to the organization the importance of conforming to the Quality Policy and support achievement of the Quality ~~and GMP~~ Objectives;

e) provide evidence of its commitment to meeting and monitoring ongoing conformance to the requirements of this Standard, the relevant statutory and regulatory requirements, and customer expectations;

f) ensure a timely and effective communication and escalation process to top management exists to raise issues of conformance to this Standard that may impact the quality of the finished excipients or changes to regulatory requirements ~~to top management~~ (see ~~5.5.3~~7.4); ~~and~~

g) ensure management reviews are conducted on a regular basis~~.~~; and

NOTE — Top management has overall responsibility for the quality management system; however, some tasks may be delegated to others.

~~5.2 Customer focus~~

h) ~~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~~2 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~~9.3).

5.3 Organizational Roles, responsibilities and authorities

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

A quality unit independent from production shall be responsible for conformance of the manufacture of the excipient with the requirements of this Standard, including but not limited to:

- approving and assessing the ongoing qualified status of suppliers of materials, components and services that may impact the quality of the finished excipient;
- approving or rejecting raw materials, packaging components, intermediates and finished excipients;
- ensuring production records are reviewed to confirm that the process remains in a state of control, and to identify discrepancies including errors during operations that require investigation;
- approving the documented results of investigations into manufacturing deviations or discrepancies, test or measurement errors and failures, and complaints;
- ensuring corrective and preventive actions are implemented and effective;
- reviewing proposed changes that have the potential to impact excipient quality (see 8.5.6);
- approving changes that have the potential to impact excipient quality prior to implementation (see 8.5.6);
- approving or rejecting the excipient if it is manufactured, processed, packaged, or held under contract by another company;
- developing and implementing an internal audit program; and
- ensuring that providers of outsourced services have agreed to comply with the relevant sections of the Standard.

The Quality Unit may delegate some aspects of these activities if justified as appropriate, however, they shall retain ultimate responsibility for oversight and approval of all delegated activities, applicable controls, and final decisions.

An organization chart by function shall show inter-departmental relationships as well as relationships to top management of the organization.

~~5.4~~6 Planning

6.1 Actions to Address Risks and Opportunities

The organization shall use the internal and external factors identified in 4.1 and the requirements and expectations of the interested parties in 4.2 to develop a quality management system that provides assurance the excipient(s) meet the expectations of the interested parties. The organization shall identify and document the risks that could impact the effectiveness of the quality management system and the quality of the excipient (for example 7.1.2, 7.1.3, and 7.1.4). These risks shall be regularly reviewed, and actions taken in proportion to their potential impact on the quality management system, the quality of the excipient, and/or the expectations of the interested parties. The effectiveness of the actions shall be reviewed during Management Review (see 9.3). Improvement to the quality management system and reduction of risks to excipient quality shall also be considered and implemented where appropriate (see 10.3)

Note: Risks to excipient quality can affect the excipient itself (e.g. contamination) or be the result of defects in the quality management system (e.g. inability to trace a batch).

~~5.4.1~~6.2 Quality objectives and Planning to Achieve Them

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 those Quality Objectives. Quality Objectives shall be deployed throughout the organization and shall be understood, measurable, and consistent with the Quality Policy.

~~5.4.2~~6.3 ~~Quality management system planning~~ Planning of changes

~~Top management shall provide adequate resources to ensure conformance to the provisions of this Standard.~~

Changes to the quality management system shall be performed in a structured manner with consideration for, as appropriate, the:

1. intended changes can be realized
2. risks and opportunities arising from the changes have been evaluated
3. impact on objectives and the plan to realize them
4. changes to roles and responsibilities
5. impact of points 1 to 4 on interested parties

If it has been determined that a change impacts an interested party, then that party shall be notified.

~~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.~~

~~A quality unit independent from production shall be responsible for conformance of the manufacture of the excipients with the requirements of this Standard, including but not limited to:~~

- ~~approving and assessing the ongoing qualified status of suppliers of materials, components and services that may impact the quality of the finished excipient;~~
- ~~approving or rejecting raw materials, packaging components, intermediates and finished excipients;~~

~~— ensuring production records are reviewed to confirm that the process remains in a state of control throughout, and to identify discrepancies including errors in operation that require investigation;~~

~~— approving the documented results of investigations into manufacturing deviations or discrepancies, test or measurement errors and failures, and complaints;~~

~~— ensuring corrective and preventive actions are implemented;~~

~~— reviewing proposed changes that have the potential to impact excipient quality (see 4.3);~~

~~— approving changes that have the potential to impact excipient quality prior to implementation (see 4.3);~~

~~— approving or rejecting the excipient if it is manufactured, processed, packaged, or held under contract by another company;~~

~~— developing and implementing an internal audit program; and~~

~~— ensuring that providers of outsourced services have agreed to comply with the relevant sections of the Standard.~~

~~The Quality Unit may delegate some aspects of these activities if justified as appropriate, however, they shall retain ultimate responsibility for oversight and approval of all delegated activities, applicable controls, and final decisions.~~

~~An organization chart by function shall show inter-departmental relationships as well as relationships to top management of the organization.~~

~~5.5.2 Management representative~~

~~A member of the organization's management shall be appointed and given authority by top management to ensure the provisions of this Standard are properly implemented. The management representative shall have demonstrated qualifications and experience. The management representative shall hold a senior position in the quality unit unless otherwise justified.~~

~~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.~~

~~Based on risk assessment, top management shall be notified in a timely manner of events that affect excipient quality and shall support appropriate corrective and preventive actions, 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. These reviews 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:~~

- ~~action items from the previous management review;~~
- ~~results of internal and external audits;~~
- ~~excipient conformity and process performance;~~
- ~~customer feedback regarding the organization's performance;~~
- ~~customer complaints;~~
- ~~status and review of corrective and preventive actions;~~
- ~~changes to the excipient quality management system;~~
- ~~new, revised, and proposed compendial and regulatory requirements; and~~
- ~~recommendations for excipient quality management system improvement.~~

~~**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~~7 ~~Resource management~~ Support

7.1 Resources

The persons needed to effectively operate the GMP and quality management system and ensure control of the organization's processes shall be confirmed, for example in the management review (see 9.3).

~~6.1~~7.1.1 ~~Provision of resources~~ General

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.

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.

~~6.2~~7.1.2 ~~Human resources~~ People

~~6.2.1~~7.1.2.1 General

Personnel who have a direct or significant impact on excipient quality shall have job descriptions and defined responsibility and authority. Personnel performing and supervising 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 the education, training, and experience or any combination thereof that qualifies them 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 having the~~

~~potential to affect excipient quality or elements of this Standard. These employees including their supervisors shall be adequately trained prior to carrying out their assigned duties. Training shall include, at a minimum:~~

- ~~the particular operations the employee performs;~~
- ~~the elements of this Standard as they relate to the employee's duties;~~
- ~~the elements of hygienic practices for personnel whose activities or responsibilities have the potential to result in contamination of the excipient including an explanation of how these are a hazard to the end user/patient;~~
- ~~the reporting of significant failures and deviations from procedures including the impact deviations from procedures may have on excipient quality; and~~
- ~~the importance of consistent adherence to good manufacturing practice, and their role in assuring drug product performance and patient safety.~~

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

~~6.2.3~~7.1.2.2 Hygienic practices

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

- the personnel, including their hygiene, any apparent illness or open lesions, and their attire;
- the equipment used by the personnel;
- the opportunity for loose items to fall into the excipient;
- the access of unauthorized personnel to designated limited access areas; and
- the ~~storage and use of~~ areas where food, drink, personal medication, tobacco products, or similar items are stored or may be used.

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

Personnel shall be instructed to report to supervisory personnel any health conditions that may ~~have an adverse effect on excipients.~~ may adversely affect safety and quality of the excipient.

~~6.3~~7.1.3 Infrastructure

The infrastructure shall be operated, cleaned, and maintained in accordance with this Standard to ensure excipient quality and the avoidance of contamination or mix-ups.

~~6.3.1~~7.1.3.1 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 expressed, intended use of the excipient (see ~~7.2~~7.1.3) 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 shall consider the following, at a minimum, to identify where the excipient is at risk of contamination:

— state of repair of the building and facility;
— suitable size, construction, and location;

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

— 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; and
— presence of environmental contaminants, including microorganisms.

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

~~6.3.2~~7.1.3.2 Equipment

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

— maintained in a good state of repair;

— of suitable size, construction, and location to facilitate cleaning, maintenance, and correct operation, commensurate with the type of processing;

— 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; and

— equipment such as change parts, utensils and hoses shall be cleaned and stored in such a way as to render them fit for use in the manufacture of excipients.

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

~~6.3.2.1~~7.1.3.3 Equipment design and construction

New installations or replacement equipment shall be designed and constructed to minimize the possibility of contamination and shall be ~~commissioned~~ demonstrated before use to ~~ensure it is~~ 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 ~~materials~~ components, intermediates, or finished excipients shall be identified. When risks are identified, they shall be mitigated so as to minimize the possibility of contact with the process stream. Where contact is possible, materials suitable for food contact shall be used unless otherwise justified.

~~6.3.2.2~~7.1.3.4 Equipment maintenance

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

There shall be chronological records of the use, maintenance, and associated cleaning of equipment coming into contact with the process stream. There shall be a ~~standard~~ written procedure for the storage of equipment not in use.

~~6.3.2.3~~7.1.3.5 Computer systems

The organization shall document the following for computer systems that impact excipient quality and/or quality management system:

— consistent operation of the system;

— prevention of unauthorized access;

— ~~assessment of~~ 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; and

— provisions to assure the maintenance of data and data integrity.

~~6.3.3~~7.1.3.6 Utilities

The organization shall conduct a risk assessment considering the risk to excipient quality from utilities intended or with the potential to come into contact with the excipient (including ~~e.g.,~~ utilities can include nitrogen, compressed air, steam, water~~, etc.~~). Control measures shall be implemented to mitigate the identified risks. Utilities coming into direct contact with the excipient during its manufacture or surfaces that could contact excipients shall have documented specifications to assure that the utility is suitable for its intended use.

~~6.3.4~~7.1.3.7 Water

Unless otherwise justified, water shall, at a minimum, meet the WHO Guidelines for Drinking-Water Quality, 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, shall be consistent with the desired excipient quality standards but at a minimum, meet the WHO Guidelines for Drinking-Water Quality, 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. The water purification system and process shall be specified, and the quality of the water monitored and controlled within appropriate microbiological and chemical limits based on intended use of the excipient. Where there is water available of multiple qualities, provision shall be made to avoid mix-up.

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

7.1.4 Environment for the operation process

~~6.4~~7.1.4.1 Work environment

The organization shall conduct a risk assessment to identify areas in which the excipient is at risk for contamination from exposure to the work environment.

The work environment shall be managed and controlled to minimize risks of excipient contamination.

The documented risk assessment shall include marketed use (see 4.1), customer requirements (see ~~7.2.1~~8.2.2), and, as applicable, shall consider the following ~~controls~~:

- air handling systems;
- ~~special~~ controlled environments;
- cleanliness and sanitary conditions;
- waste segregation and disposal;
- pest control; and
- other risk assessments required by this Standard (see ~~6.2 and 6.3~~ 7.1.2 and 7.1.3).

A documented risk assessment shall be carried out to determine the necessary controls. Controls shall be implemented, monitored and documented.

~~6.4.1~~7.1.4.2 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~~7.1.4.3 Controlled environment

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

Where an inert atmosphere is required, the gas shall be treated as a raw material as defined in ~~7.4.3~~8.4.2.

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~~7.1.4.4 Cleaning and sanitary conditions

~~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.~~

Where the risk assessment (see ~~6.3.1~~ 7.1.3.1) 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.

7.1.4.5 Waste segregation and disposal

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~~7.1.4.6 Pest control

A pest control program shall be implemented. The elements of the pest control program shall be determined by risk assessment.

~~6.4.5~~7.1.4.7 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~~7.1.4.8 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~~7.1.4.9 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.

Based on the results of the risk assessment in ~~6.2.3~~7.1.2.2, facilities for showering and/or changing clothes shall be provided.

7.1.5 Monitoring and measuring resources

The organization shall use calibrated and/or verified measuring and test devices. Such measuring and test devices shall have the appropriate specificity and sensitivity. Records of calibration and/or 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 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 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.

7.1.6 Organizational knowledge

The organization shall demonstrate that it has the knowledge to meet the needs of the interested parties, manufacture the excipient, and support the quality management system. The organization shall have knowledge of the regulations concerning the use of the excipients supplied. When changes are applied to the quality management system (see 6.3) or the excipient (see 8.5.6) the organization shall perform a gap analysis between the current knowledge and what is required. The organization shall acquire the new knowledge.

> Note: Knowledge would be aligned to the claims made about excipient, its intended uses and the countries in which it is marketed.

7.2 Competence

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

at a minimum:

- the particular operations the employee performs;
- the elements of this Standard as they relate to the employee's duties;

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

Where third party personnel carry out GMP activities these individuals shall be trained to the same extent as employees for the activity that they were contracted to complete.

7. 3 Awareness

The organization shall ensure employees are aware of the risks to excipient quality from their activities prior to carrying out their duties. Risk awareness training shall include, at a minimum:

- the elements of hygienic practices for personnel whose activities or responsibilities have the potential to result in contamination of the excipient including an explanation of how these are a hazard to the end user/patient;
- the reporting of significant failures and deviations from procedures including the impact deviations from procedures may have on excipient quality;
- the importance of consistent adherence to good manufacturing practice, including the integrity of data, and their role in assuring drug product performance and patient safety.

7. 4 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.
Based on risk assessment, top management shall be notified in a timely manner of events that affect excipient quality and shall support appropriate corrective and preventive actions, in accordance with a documented procedure.

7.5 Documented Information

7.5.1 General

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

The use of appropriate quality risk management principles shall be used to assess changes to the quality management system.

NOTE — Quality risk management 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 shall be included in the quality management system:

a) Quality Objectives;

b) documents and records required by this Standard and any other documents necessary for the effective planning, operation and control of the processes; and

c) a documented risk assessment that defines and justifies when the as/if/where applicable clauses in this Standard are not implemented.

NOTE 1 - 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.

NOTE 2 - Documentation may be in any form or type suitable for long-term storage and retrieval and must be readable.

NOTE 3 - 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 quality management system and its processes,
- management responsibilities,
- the scope of application (including the point in the manufacturing process at which all of the requirements of this standard are applied),
- the Quality Policy,
- references 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 quality management requirements contained in this Standard.
- justification why the provisions of a clause does not apply.

7.5.2 Creating and Updating

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 7.5.3.

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, version controlled, 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.

Procedures that impact excipient quality shall have a defined owner and be reviewed and approved by the quality unit before issue including changes to these documents (see 5.3).

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 that given by a hand-written signature.

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

7.5.3 Control of Documented Information

The organization shall establish and maintain a documented procedure for the identification, collection, indexing, filing, storage, maintenance, protection, retention time, and destruction 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 stringency of controls as those required for other records. Pertinent subcontractor quality data shall meet the provisions of this section.

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 one year past the excipient's expiry or two years past the retest date. If the manufacturer does not stipulate an expiry or retest/re-evaluation interval, the record retention period shall be a minimum of five years from the date of manufacture. Documented procedures shall be implemented to ensure control of COAs.

~~7~~8 ~~Excipient realization~~ Operation

~~7~~8.1 ~~Planning of excipient realization~~ Operational planning and control

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:

— human resources, equipment, and facilities for storage and testing used in the manufacture and supply of the excipient;

— testing programs for materials used in the manufacture of the excipient and the finished excipient that include appropriate specifications, sampling plans, and test and release procedures; and

— environmental and hygiene control programs to minimize the potential for contamination of the excipient.

The record system shall demonstrate that 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~~8.2 ~~Customer-related processes~~ Requirements for products and services

~~7.2.1 Determination of requirements related to the excipient~~

~~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 documented prior approval from the customer shall be determined.~~

~~**7.2.2 Review of requirements related to the excipient**~~

~~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~~8.2.1 Customer communication

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

The organization shall define how potentially significant changes (see 8.2.3) or deviations that impact excipient quality (see 8.5.5) are assessed and communicated to customers (see 8.5.6).

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

~~Deviations that may impact excipient quality and which become known after delivery of the excipient shall be evaluated and communicated to customers. The impact of such deviations shall be assessed and provision made for return of excipient as necessary (see 8.3).~~

~~7.2.3.1~~8.2.1.1 Customer complaints

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

8.2.2 Determination of requirements related to the excipient

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 documented prior approval from the customer shall be determined.

8.2.3 Review of requirements related to the excipient

The organization shall review the requirements identified in 8.2.2 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 8.2.2 are changed, this review shall be repeated before supply recommences.

8.2.4 Changes to requirements for products and services

Top management shall establish and maintain a robust change control program under the quality management system. This program shall be designed to ensure that excipient quality is assessed and maintained in accord with principles of quality risk management when changes are planned and implemented, respectively.

87.3 Design and development (out of scope)

78.4 ~~Purchasing~~ Control of externally provided processes, products, and services

78.4.1 ~~Purchasing process~~ General

The organization shall establish a documented system for selecting, approving, and reapproving suppliers of materials and services. The organization's quality unit shall undertake a risk assessment to determine materials and services that have the potential to impact excipient quality and approve such suppliers. Materials shall be purchased against a mutually agreed specification.

For such materials and services, the supplier shall have an agreement to notify the organization of significant changes. If an agreement cannot be obtained, a risk assessment shall be performed and a written justification and mitigation plan for continued use of the supplier shall be implemented.

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

Where manufacturing, testing, or other operations that may affect excipient quality are outsourced, the responsibilities for excipient quality and control measures applicable to this Standard shall be defined and documented.

~~**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:~~

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

~~7.4.3~~8.4.2 ~~Verification of purchased product~~ Type and extent of control

The organization shall establish procedures to verify, approve, and release 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 that the measurements reported on the supplier Certificate of Analysis for each lot meet the agreed specification. For packaging components, the organization shall verify the Certificate of Conformance references the current agreed specification. 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 method for obtaining representative samples and using procedures designed to prevent contamination and cross-contamination.

The organization shall establish controls to assure materials delivered in bulk or returned and reused containers are free from contamination and fit for its intended purpose.

8~~7~~.5 Production and service provision

8~~7~~.5.1 Control of production and service provision

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

— production instructions that describe the manufacture of the excipient and that establish records ~~providing~~ 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); and

— the identification and traceability of equipment used, its maintenance, and cleaning.

— equipment and utensil cleaning and sanitization procedures justifying the method and frequency of cleaning, establishing criteria for determining effectiveness, and requiring chronological records of cleaning activities as noted above; the cleaning status of equipment shall be known;

— state of process control is confirmed using documented in-process testing;

— packaging and labeling control procedures shall ensure that the material is traceable. Provisions shall ensure that the containers are not mislabeled as to lot and/or product; and

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

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

~~7.5.2~~8.5.1.1 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 same 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, intensified monitoring and testing, development and scale-up reports, etc.

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

~~7.5.3~~8.5.2 Identification and traceability

The organization shall establish a system to identify the 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 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, labeling shall include:

- the name of the excipient and, if applicable, grade;
- the organization's name and identity of the manufacturing site;
- the batch number;
- storage conditions, if other than ambient (i.e., uncontrolled temperature and humidity); and
- expiration date or retest date.

NOTE — These requirements can be met by codes on the label.

~~7.5.4~~8.5.3 ~~Customer property~~ Property belonging to customers and external providers

The organization shall establish and maintain procedures for verification, storage, and maintenance of customer-supplied materials intended for incorporation into or packaging of the excipient designated for that 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/or 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~~8.5.4 Preservation of excipient

The organization shall define and justify the conditions for the handling and storage of materials (see ~~7.5.3~~8.5.2) so their identity, quality, and conformance to specification are not affected within their shelf life or retest/re-evaluation interval. Records of storage conditions shall be maintained when such conditions may impact the material's quality characteristics. Deviations from specified storage conditions shall be assessed and documented.

~~7.5.5.1~~8.5.4.1 Raw material packaging systems

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

— provide suitable protection against deterioration, contamination with foreign substances, chemical and/or microbiological contamination; and

— ensure that identification labels remain legible.

~~7.5.5.2~~8.5.4.2 Excipient packaging systems

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

— documented specifications;

— documented evidence that the packaging does not adversely impact quality (e.g., packaging is not reactive, additive, or absorptive);

— documented cleaning procedures (where containers are reused);

— tamper-evident seals, unless written justification demonstrates that it is not feasible; and

NOTE — 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 and, where feasible, accounted for by the excipient manufacturer and should not be reusable once the seal is broken.

— compliance with relevant regulatory requirements.

Containers shall be stored so as to protect their cleanliness. Where reusable excipient containers are returned, the organization shall undertake a risk assessment and establish appropriate controls for their further use. Procedures shall ensure all previous labels are removed or completely obliterated.

~~7.5.5.3~~8.5.4.3 Excipient delivery

Where contractually specified, protection shall extend to include delivery to the final destination. ~~Suppliers of transport services shall be provided with the required transport controlled conditions in order for them to maintain required conditions.~~ Where controlled conditions are required to maintain excipient quality during transport, suppliers of transport services shall be provided with instructions for the required conditions.

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

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/re-evaluation interval as supported by stability data (see ~~8.2.4.7~~ 9.1.4.7).

Distribution records of excipient shipments to the initial customer, including identification and traceability, shall be maintained and shall 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; and
— date of shipment.

~~7.6 Control of monitoring and measuring equipment~~

~~The organization shall use calibrated and/or verified measuring and test devices. Such measuring and test devices shall have the appropriate specificity and sensitivity. Records of calibration and/or 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 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 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.~~

8.5.5 Post-delivery activities

Deviations that may impact excipient quality and which become known after delivery of the excipient shall be evaluated and communicated to customers. The impact of such deviations shall be assessed and provision made for return of excipient as necessary (see 8.7).

8.5.6 Control of changes

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 organization shall define the criteria for a significant change (see 3.69). The evaluation and approval of planned changes shall occur prior to the implementation of the changes. Upon implementation, the effectiveness of a change shall be confirmed. The quality unit shall approve any changes that based on risk assessment may impact the quality of the excipient. There shall be a written procedure for determining which changes to communicate to customers, as well as a mechanism for communicating changes. Significant changes shall be communicated with sufficient notice prior to implementation as is reasonably practical to customers (see 8.2.1) and, as applicable, regulatory authorities. The customer shall be informed prior to the first shipment of the excipient after the change is implemented. Documentation generated for change control shall be retained (see 7.5.3).

8.6 Monitoring and measurement of product

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

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

— non- compendial analytical tests used as an alternative to compendial tests shall be demonstrated to be at least equivalent to those in the compendia;

— the excipient shall comply with applicable monographs, general chapters and notices; and

— responsibility for monitoring those pharmacopoeia or official compendium shall be assigned.

NOTE 1 — The US Federal Food, Drug, and Cosmetic Act recognizes official compendia including the United States Pharmacopeia (USP) and National Formulary (NF).

NOTE 2 — The USP-NF is legally comprised of 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.

8.6.1 Finished excipient testing and release

Measures for verification of excipient quality shall be performed and recorded to confirm that the excipient conforms to documented specification.

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

8.7 Control of non-conforming materials

Raw material, intermediate, or finished excipient not meeting its specification shall be clearly identified and controlled to prevent inadvertent use or release for sale. Procedures shall exist for the evaluation and appropriate disposition of nonconforming raw materials, intermediates and excipients. There shall be procedures to prevent shipment of excipients that would be unacceptable to certain customers, when a customer-specific requirement is not met.

For a non-conforming excipient that is already in distribution, there shall be a documented procedure defining how the retrieval shall be conducted and recorded.

8.7.1 Investigation of non-conforming finished excipient

Failure of a batch to meet specifications for the excipient grade being produced, including failure to meet a customer-specific requirement, shall be investigated to identify the root cause, impact on other batches/products, and appropriate corrective and preventative actions (see 10).

Once the root cause is identified, corrective and/or preventative action shall be taken to bring the process back into a state of control (see 8.5.6 and 10). A record of each incidence of non-conformance shall be documented and maintained. The potential impact of any change on validation shall be assessed.

NOTE — 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 Standard meets requirements of the general sales specification(s) but not an individual customer specification(s) it may still be sold to those customers for whom it does meet their specification(s).

8.7.2 Disposition of non-conforming finished excipient

Upon the conclusion of the investigation as described in 8.7.1, the quality unit shall 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 8.7.3 or 8.7.4);
- released as a non-pharmaceutical grade material; or
- destroyed.

8.7.3 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.

8.7.4 Reworking

Reworking is a change under the provisions of change control in this Standard (see 8.5.6) 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:

- additional testing to monitor and control the reworking;
- additional acceptance criteria for the reworked excipient;
- impact on stability or the validity of the retest/re-evaluation interval;
- composition profile changes as a result of reworking;
- performance of the excipient; and
- 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 specification and characteristics. The evaluation shall be approved by the quality unit.

When blending is used for reworking, the resultant product shall 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 Standard.

8.7.5 Returned excipient

There shall be procedure(s) for the evaluation, holding, testing, reprocessing, and reworking of returned excipient.

Returned excipients shall 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 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. The excipient shall not be released if there is any reason to believe that container integrity or excipient quality may have been compromised.

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~~9 ~~Measurement, analysis and improvement~~ Performance evaluation

9.1 Monitoring, measurement and analysis

~~8.1~~9.1.1 General

The organization shall evaluate the performance and the effectiveness of the Quality Management system. The organization shall plan and implement the monitoring, measurement, and improvement activities required to ensure conformity of the quality management system to this Standard. The organization shall retain appropriate documented information as evidence of the results.
~~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**~~**9.1.2 Customer satisfaction**

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

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

~~**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:~~

- ~~determination of the effectiveness of quality activities;~~
- ~~compliance with procedures and processes described by the quality management system;~~
- ~~schedules based on findings from previous audits, performance measures (see 8.2.3), and the potential impact of the activity to finished excipient quality;~~
- ~~provisions for follow-up actions;~~
- ~~positive findings that support the effective implementation of GMP; and~~
- ~~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 without undue delay on each nonconformance found.~~

9.1.3 Analysis of data

The organization shall define methods for evaluating:

- the effectiveness of its quality management system;
- the ability to consistently produce conforming excipients;
- excipient nonconformance with this Standard, customer complaints, deviations, etc.; and
- supplier nonconformance.

The organization shall use results and trends to identify opportunities for improvement (see 9.3 and 10.1).

~~**8.2.3**~~**9.1.4 ~~Monitoring and measurement of processes~~ Analysis and evaluation**

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

Where there is the potential to impact excipient quality, methods used to verify that the processes are in control shall be documented, used, and the results recorded. The organization shall identify opportunities for improvements through the measurement and analysis of product and process trends.

~~Where there is the potential to impact excipient quality, methods used to verify that the processes are in control shall be established and documented.~~

~~Regular review of key indicators, process performance, 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 provide documentation to support the test methods and procedures used to verify that the excipient meets specification, and that the methods are suitable for their intended purpose.~~

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

~~— non- compendial analytical tests used as an alternative to compendial tests shall be demonstrated to be at least equivalent to those in the compendia;~~

~~— the excipient shall comply with applicable monographs, general chapters and notices; and~~

~~— responsibility for monitoring those pharmacopoeia or official compendium shall be assigned.~~

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

~~NOTE 2 — The USP-NF is legally comprised of 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~~9.1.4.1 Laboratory controls

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

- data to enable identification and traceability of samples which are used to determine batch status;
- record of sample preparation in conformance with test requirements;
- traceability to the test method used;
- a record of raw data generated during each test;
- a record of calculations performed in connection with each test;
- test results and how they compare with established specification; and
- a record of the person who performed each test and the date(s) the tests were performed.

The organization shall document the provisions to assure the maintenance of data and data integrity.

~~8.2.4.1.2~~9.1.4.2 Laboratory procedures

There shall be documented procedures for the following:

— 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 or date of preparation, and the assigned expiration or restandardization date;

— provisions for the receipt, storage, and use of primary reference standards; and

— 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**~~

~~Measures for verification of excipient quality shall be performed and recorded to confirm that the excipient conforms to documented specification.~~

~~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~~9.1.4.3 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 non-conforming, the organization shall conduct a thorough investigation of all out of specification (OOS) test results[11], starting with a prompt laboratory investigation, according to a documented procedure. The findings of the investigation, including conclusions and follow up actions, shall be recorded.

The OOS procedure shall provide detailed steps for conducting an investigation. The procedure shall define appropriate provisions for investigation of original test results, including but not limited to:

— criteria for retesting original sample;

— criteria for resampling; and

— 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 shall be used to determine batch disposition.

~~8.2.4.4~~9.1.4.4 Retained samples

A representative sample of each batch of the excipient shall be retained unless otherwise justified and documented. The retained sample retention period shall be justified.

Retained samples shall be stored in a secure location, readily retrievable, and under conditions consistent with specified storage conditions.

[11] FDA Guidance for Industry: *Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production*, October 2006.

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

~~8.2.4.5~~9.1.4.5 Certificates of analysis

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

The Certificate of Analysis shall include, at a minimum:

— excipient name (trade name), and, if applicable, grade, and compendial name and 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 Certificate of Analysis then this information shall be communicated separately;

— date of manufacture;

— batch number;

— expiration date or retest date, and, if previously retested, the date it was retested;

— statement of conformance to the required specification;

— statement of compliance to GMP as defined by this Standard (may be otherwise communicated with the customer);

— analytical results representative of the batch; if not based on testing of a sample of the finished excipient the basis of the results shall be communicated to the customer, (see NOTE below for alternatives to finished excipient testing, as appropriate);

— acceptance criteria;

— reference to the analytical method used; and

— name and title of person whose physical signature appears on the Certificate of Analysis or electronic signature statement.

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

~~8.2.4.6~~9.1.4.6 Excipient composition

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

~~8.2.4.7~~9.1.4.7 Stability and expiry/retest periods

The stability of the excipient shall be documented.

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

— historical data; or
— stability studies.

An expiry or retest/re-evaluation interval for the excipient shall be determined, justified, and communicated to the customer.

NOTE — See guidance as provided by the *IPEC Excipient Stability Program Guide*.

9.2 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:

- determination of the effectiveness of quality activities;
- compliance with procedures and processes described by the quality management system;
- schedules based on findings from previous audits, performance measures (see 9.1.4), and the potential impact of the activity to finished excipient quality;
- provisions for follow-up actions;
- positive findings that support the effective implementation of GMP; and
- 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 without undue delay on each nonconformance found.

~~**8.3 Control of nonconforming product**~~

~~Raw material, intermediate, or finished excipient not meeting its specification shall be clearly identified and controlled to prevent inadvertent use or release for sale. Procedures shall exist for the evaluation and appropriate disposition of nonconforming raw materials, intermediates and excipients. There shall be procedures to prevent shipment of excipients that would be unacceptable to certain customers, when a customer-specific requirement is not met.~~

~~For a non-conforming excipient that is already in distribution, there shall be a documented procedure defining how the retrieval shall be conducted and recorded.~~

~~**8.3.1 Investigation of non-conforming finished excipient**~~

~~Failure of a batch to meet specifications for the excipient grade being produced, including failure to meet a customer-specific requirement, shall be investigated to identify the root cause, impact on other batches/products, and appropriate corrective and preventative actions (see 8.5).~~

~~Once the root cause is identified, corrective and/or preventative action shall be taken to bring the process back into a state of control (see 4.3 and 8.5). A record of each incidence of non-conformance shall be documented and maintained. The potential impact of any change on validation shall be assessed.~~

~~NOTE — 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 Standard meets requirements of the general sales specification(s) but not an individual customer specification(s) it may still be sold to those customers for whom it does meet their specification(s).

8.3.2 Disposition of non-conforming finished excipient

Upon the conclusion of the investigation as described in 8.3.1, the quality unit shall 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 8.3.3 or 8.3.4);
- released as a non-pharmaceutical grade material; or
- destroyed.

8.3.3 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.

8.3.4 Reworking

Reworking 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:

- additional testing to monitor and control the reworking;
- additional acceptance criteria for the reworked excipient;
- impact on stability or the validity of the retest/re-evaluation interval;
- composition profile changes as a result of reworking;
- performance of the excipient; and
- 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 specification and characteristics. The evaluation shall be approved by the quality unit.

When blending is used for reworking, the resultant product shall 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 Standard.

8.3.5 Returned excipients

There shall be procedure(s) for the evaluation, holding, testing, reprocessing, and reworking of returned excipient.

Returned excipients shall 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 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. The

~~excipient shall not be released if there is any reason to believe that container integrity or excipient quality may have been compromised.~~

~~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:~~

- ~~the effectiveness of its quality management system;~~
- ~~the ability to consistently produce conforming excipients;~~
- ~~excipient nonconformance with this Standard, customer complaints, deviations, etc.; and~~
- ~~supplier nonconformance.~~

~~The organization shall use results and trends to identify opportunities for improvement (see 5.6 and 8.5.1).~~

9.3 Management review

9.3.1 General

Top management shall hold scheduled reviews of the excipient quality management system to confirm continued conformance to this Standard. These reviews shall be documented. Any opportunities for improvement shall be assessed and implemented via the change control procedure (see 8.5.6).

NOTE — For excipient quality review requirements, see 9.1.4.

9.3.2 Review input

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

- action items from the previous management review;
- results of internal and external audits;
- excipient conformity and process performance;
- customer feedback regarding the organization's performance;
- customer complaints;
- status and review of corrective and preventive actions;
- changes to the excipient quality management system;
- new, revised, and proposed compendial and regulatory requirements; and
- recommendations for excipient quality management system improvement.

9.3.3 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.

~~8.5~~10 Improvement

~~8.5.1~~10.1 ~~Continual improvement~~ General

The organization shall undertake a periodic review, which includes data as described in ~~8.4~~9.1.3, to identify improvement opportunities in the manufacturing and quality management system processes.

10.2 Non conformity and corrective action

The organization shall establish procedures for:

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

10.3 Continual improvement

The organization shall establish procedures for:

- initiating preventive actions commensurate with the corresponding risks;
- implementing and recording changes in procedures and processes resulting from preventive action; and
- ensuring that preventive actions are implemented and effective.

The organization shall consider the results of analysis and evaluation and the output from management review to determine if there are needs or opportunities that shall be addressed as part of continual improvement (see 9.1.3 and 9.3.3).

~~**8.5.2 Corrective action**~~

~~The organization shall establish procedures for:~~

~~d) determining the root causes of nonconformance;~~
~~e) ensuring that corrective actions are implemented and effective; and~~
~~f) implementing and recording changes in procedures resulting from corrective action.~~

~~**8.5.3 Preventive action**~~

~~The organization shall establish procedures for:~~

~~— initiating preventive actions commensurate with the corresponding risks;~~

~~— implementing and recording changes in procedures and processes resulting from preventive action; and~~

~~— ensuring that preventive actions are implemented and effective.~~