

EXCiPACT

GMP Annex to ISO 9001:2015 Additional Requirements for Pharmaceutical Excipients

With additional clauses to
comply with Chinese GMP for
excipients

Based on Revision 2021

General Introduction to China GMP Annex

The Drug Administration Law of the People's Republic of China (2019 revision) defines excipients as "Substances other than the active pharmaceutical ingredient and prodrug in the drug formulation". This is similar in principle to the IPEC and EXCiPACT definition which is:

Pharmaceutical excipients are substances other than the Active Pharmaceutical Ingredient that have been appropriately evaluated for safety and are intentionally included in a drug delivery system¹.

The Chinese excipient GMP of 2006² requires that excipients required for the production of medicines have to be suitable for such use and as a result have to be made under the supervision of a quality management system that assures their quality and safety to the patient. A key principle of this GMP is that the starting point of GMP is defined in the manufacturing process and that the degree and extent of GMP is increased throughout the manufacturing process.

The Chinese Excipient regulations contain a number of additional requirements for the GMP to be applied to the manufacture of excipients which are not included in the EXCiPACT GMP annex. Hence, this annex has been designed by a team of Chinese experts to completely align the existing EXCiPACT GMP Annex with the requirements of these Chinese excipient regulations 2006.

Introduction

If the appropriate quality standards are not followed, excipients may pose a hazard to patient safety. Thus, the requirement to have a robust quality system in place that assures the quality and purity of excipients remains an imperative, particularly as events with fraudulent claims of pharmaceutical raw material purity have resulted in so many human tragedies.

Legislators and regulatory authorities globally have addressed and continue to address the weaknesses in the application of GMP to pharmaceutical excipients with the objective to minimise patient risk. China has taken this a step further and actually defined the GMP that is required for the manufacture of excipients.

A common theme all in these regulatory requirements is that the excipient user has to have knowledge of the management systems and GMP used to manufacture the excipient. As a result, excipient supplier sites could be asked to host hundreds of extra audits. In recognition of these issues the

¹ The IPEC Glossary of Terms and Acronyms, <http://www.ipec.org/node/127>

² Good Manufacturing Practice for Pharmaceutical Excipients, [2006] No. 120 issued by the SFDA, the predecessor to NMPA.

authorities in the PIC/S³ scheme have clearly stated that the excipient user (drug product manufacturer) can utilise third party audit organisations to perform the audits⁴. Thus, a third-party audit organisation may perform the audit, so reducing the burden in time and resources for both the excipient user and excipient supplier. However, for such third-party audit organisations to be accepted within the industry both the standard used to assess excipient suppliers and the competency of their auditors has to be addressed.

As a result, a group of international industry experts from European Fine Chemical Group (EFCG), International Pharmaceutical Excipients Council (IPEC) Europe, IPEC-Americas, European Association of Chemical Distributors (FECC), and Pharmaceutical Quality Group (PQG) worked together on the development of the EXCiPACT certification scheme for excipient suppliers which was launched in 2012. The GMP standard used for certification were based on the widely accepted IPEC-PQG GMP Guide for pharmaceutical excipients.

The EXCiPACT Certification Scheme provides for independent certification of manufacturers and suppliers of excipients. This is a means of ensuring patient safety and improving assurance of supplier quality, while minimising overall supply chain costs.

Many excipient suppliers are already registered to the Quality Management System standard, ISO 9001 which provides an excellent framework on which to build and develop systems suitable for the manufacture and supply of pharmaceutical excipients. ISO 9001, therefore, forms the basis for the EXCiPACT GMP standard as an annex to ISO 9001:2015. This allows excipient suppliers to be assessed to ISO 9001:2015 and the EXCiPACT GMP annex at the same time.

The remaining sections of this 2021 EXCiPACT publication cover the requirements for third party audit organisations covering both auditor competency and quality system requirements for these organisations. The auditor competency requirements are aligned with the requirements in ISO/IEC 17021-1:2015, Conformity Assessment – Requirements bodies providing audit and certification of management systems.

Scope of Annex

The scope of annex therefore applies to both excipients manufactured and used in China and those which are imported, either for use in pharmaceutical drug product manufacture in China or in final drug products which are made elsewhere. In either case conformance to the Chinese GMP regulations is required and this annex is not an alternative to a Chinese National or regional regulatory inspection.

³ <https://picscheme.org/en/picscheme>

⁴ Directive 2011/62/EU of the European Parliament and of the Council of 8 June 2011 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use, as regards the prevention of the entry into the legal supply chain of falsified medicinal products, Article 46 point (f).

The requirements of this Annex are not sufficient for the manufacture of sterile excipients, as additional controls will be required which are not within the competency requirements for EXCiPACT auditors.

All other excipients, including those derived by animal origins, co-processed and premixed excipients can be accommodated by the controls described in this Annex and would then be within the competency requirements of EXCiPACT auditors.

Presentation of Additional Requirements for China GMP

This document is based on the 2021 edition of the EXCiPACT GMP Annex. That text is presented in an unaltered format. The Additional requirements for China GMP for excipients are highlight by being placed in a shaded box, for example:

- a) the procedures and documentation required for validation activities.

Foreword to the ISO 9001 China GMP Annex

Many excipient manufacturers and distributors are already registered to ISO 9001:2015, "Quality Management Systems – Requirements", and consequently EXCiPACT has developed this Annex to that standard to allow such organisations to be assessed simultaneously to ISO 9001:2015 and to the requirements for GMP for pharmaceutical excipients. This Annex to ISO 9001:2015 is based on the current version of the Joint IPEC-PQG Good Manufacturing Practices Guide for Pharmaceutical Excipients. The guidance ("how to do") in that document has been converted to an auditable standard ("what to do") and parts already covered by ISO 9001:2015 removed, resulting in this Annex.

Organisations that manufacture and distribute excipients can choose to be certified to this Annex and the corresponding GDP Annex, together or separately, depending on their business arrangements.

The main text that follows is based on the headings in ISO 9001:2015 and details the pharmaceutical excipient GMP requirements:

Texts in Bold are ISO 9001:2015 Headings

Standard Texts are GMP requirements

Italicised texts are taken directly from ISO 9001:2015 to provide context to the Annex statements which immediately follow.

For full comprehension, this Annex should be read in conjunction with ISO 9001:2015 which can be purchased via www.iso.org.

This version of EXCiPACT GMP annex is based on a re-alignment of the clauses in the EXCiPACT GMP Annex 2012 to match the clause structure in ISO 9001:2015. Minor revisions to the text have been made to fit ISO 9001:2015 requirements and to incorporate learning from the implementation of the EXCiPACT certification Scheme.

0 Introduction

This document is an annex to ISO 9001:2015. Organisations requiring certification to this Annex shall hold an ISO 9001:2015 certificate, issued under accreditation of an International Accreditation Forum member, National Accreditation Body and covering the scope of manufacture and/or distribution of relevant excipient products. For organisations not holding a current ISO 9001:2015 certificate, and for recertification, assessment against the requirements of this Annex and ISO 9001:2015 may be conducted simultaneously.

Note: Increasingly users of pharmaceutical excipients are required by regulatory authorities to include audits of their suppliers in their supplier qualification process. Although the objective of this standard is to reduce

the number of these audits, EXCiPACT certification might not always be suitable for every customer's supplier qualification requirements. Therefore, audits at suppliers of excipients critical to the users' application may still be necessary.

1.1 General

Excipient manufacture shall be carried out in accordance with Good Manufacturing Practice (GMP) principles consistent with this Annex. The objective of excipient GMP is to ensure that the manufacture of excipients results in a consistent material with the desired appropriate quality characteristics, to assure product integrity and consistent quality, to avoid product contamination, and to ensure that appropriate records are maintained.

Throughout this document, references to "GMP for pharmaceutical excipients" will be referred to as "GMP" and "excipients" to mean "pharmaceutical excipients".

An excipient can only be assigned as pharmaceutical grade when it is in compliance with a pharmacopoeial specification (if existing for the specific excipient) and/or appropriate regulatory requirements and is manufactured, repackaged, and handled in accordance with the appropriate excipient GMP and GDP (e.g., EXCiPACT GMP, EXCiPACT GDP, IPEC-PQG Excipient GMP Guide, IPEC Excipient GDP, WHO Excipient GTDP, NSF/IPEC/ANSI 363-2016).

This document includes additional requirements to ISO 9001:2015 that support the application of GMP to the manufacture of excipients. The section headings are consistent with those in ISO 9001:2015. When a list does not start with "a)" then it is an addition to the text of the corresponding paragraph in ISO 9001; e.g., in 5.11, where the list starts with "k)". Where reference is made to ISO 9001 this means ISO 9001:2015.

1.2 Quality Management principles

No additional requirements.

1.3 Process approach

1.3.1 General

No additional requirements.

1.3.2 Plan-Do-Check-Act cycle

No additional requirements.

1.3.3 Risk-based thinking

The manufacture and origin of excipients is exceptionally variable, therefore a “one size fits all” approach to the definition of excipient GMP is not possible. In such circumstances, utilising risk assessments by the excipient manufacturer will identify those aspects of manufacture that require the implementation of GMP controls to minimise the threats to excipient quality, patient safety and regulatory compliance. Therefore, widespread use is made in this Annex for the excipient manufacture to undertake and document risk assessments and their action plans. These risk assessments and the resulting outputs of any actions identified form a key part of the quality management system and its documentation.

There are many suitable risk assessment approaches and tools, and the manufacturer may utilise those best suited to their circumstances.

Note: The methodologies detailed in ICH Q9 are particularly applicable to a pharmaceutical setting.

1.4 Relationship with other Management System Standards

No additional requirements.

Quality Management and GMP systems – requirements

1 Scope

The scope of this Annex is the addition of GMP requirements for excipients to ISO 9001:2015. These principles are to be applied from the point in the manufacturing process where GMP has been determined to begin. (See Clause 4.3).

Note: The requirements of this Annex are not sufficient for the manufacture of sterile excipients, as additional controls will be required.

The Annex and its Use

For guidance on the requirements in this Annex, consult the current edition of the IPEC-PQG Good Manufacturing Practices Guide for Pharmaceutical Excipients.

2 Normative References

ISO 9001:2015, Quality Management Systems – Requirements,
WHO, Guidelines for Drinking-water Quality, 4th edition, 2011³.

Note: See also Appendix 2 for other references.

³ http://www.who.int/water_sanitation_health/publications/2011/dwg_guidelines/en/

3 Terms and Definitions

See Appendix 1 "Definitions and Glossary".

4 Context of the Organisation

4.1 Understanding the organisation and its context

The organisation shall define the intended use(s) of the excipients. These definitions shall be recorded.

External and internal issues shall include outsourced activities, (see 8.4) that can affect excipient quality and for which the organisation has control and responsibility.

4.2 Understanding the needs and expectations of interested parties

The requirements arising from the regulations concerning the manufacture and supply of excipients on the Chinese Market shall be integrated into the quality management and GMP systems.

Excipients intended for supply in China shall be

- registered and maintained on the NMPA portal, and
- shall be manufactured and supplied in accordance with the submitted dossier

Note:

The regulatory authorities governing pharmaceutical products

should be included as interested parties, even in cases where they have no direct jurisdiction over the excipient supplier.

4.3 Determining the scope of the Quality Management System

This Annex includes requirements additional to those for ISO 9001 certification purposes and enables organisations to demonstrate conformity to GMP for the manufacture of excipients.

The organisation shall establish and maintain supporting documentation or references including:

- a) a definition of the extent to which this Annex applies to its quality management system and its business processes,
- b) an identification and justification of the point at which the full requirements of this Annex apply to each manufacturing process for each excipient within scope. (See Section 1).

Note: The GMP principles in this Annex may be applied earlier than this point in the excipient manufacturing processes.

4.4 Quality Management System and its processes

4.4.1

No additional requirements.

4.4.2

No additional requirements.

4.4.3

The quality management system documentation shall include:

- b) the organisation's overall intentions and approach to GMP,
- c) documented procedures required for conformance to this Annex,
- d) documented risk assessment(s) that defines and justifies when the "if/as applicable" clauses in this Annex are not implemented.
- e) the procedures and documentation required for validation activities.

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

- a) define the responsibility for quality and the control measures within the quality management system (see also 8.4),
- b) demonstrate that the applicable GMP principles in accordance with this Annex are applied to those operations.

Note: Quality risk management can be useful for identifying and

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prioritising areas for continual improvement.

5 Leadership

5.1 Leadership and commitment

5.1.1 General

Top management shall demonstrate leadership and commitment with respect to the quality management system by:

- k) ensuring that GMP objectives are established,
- l) communicating to the organisation the importance of conforming to the requirements of this Annex.

5.1.2 Customer focus

Top management shall demonstrate leadership and commitment with respect to customer focus by ensuring that:

- d) customer requirements related to GMP for pharmaceutical excipients are determined, understood, agreed with the customer, and met.

5.2 Policy

5.2.1 Establishing the Quality Policy

Top management shall establish, implement, and maintain a quality policy that:

- e) includes a commitment to comply with GMP requirements.

5.2.2 Communicating the Quality Policy

No additional requirements.

5.3 Organisational roles, responsibilities, and authorities

Top management shall designate a member of the site's management who, irrespective of other responsibilities, shall have responsibility and authority that includes:

- a) ensuring that processes needed for the quality management system are established, implemented, and maintained,
- b) reporting to top management on the performance of the quality management system and any need for improvement,
- c) ensuring the promotion of awareness of customer requirements throughout the organisation,
- d) ensuring the promotion and awareness of regulatory requirements throughout the organization, including compliance to Chinese excipient regulations

Top management shall assign the authority and responsibility for:

- f) a Quality Unit independent from production which shall be responsible at a minimum for:

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- ensuring quality critical activities are identified and undertaken as defined,
 - approving suppliers of quality critical materials and services,
 - approving or rejecting raw materials, packaging components, intermediates, and finished excipients,
 - reviewing batch records to ensure that significant deviations have been fully investigated and documented,
 - releasing the finished excipient,
 - ensuring corrections, corrective actions, and actions to address risks and opportunities are implemented,
 - reviewing and approving significant changes (see 6.3), including those to quality critical equipment, processes, specifications, procedures, and test methods,
 - approving the results of investigations into deviations from process instructions, test or measurement failures, and complaints,
 - approving or rejecting the excipient if it is manufactured, processed, packaged, or held under contract by another company,
 - developing and implementing an internal audit programme,
 - ensuring that providers of outsourced services have agreed to comply with the relevant sections of this Annex.
- approving validation plans, protocols and reports.

These responsibilities may be delegated by the Quality Unit if appropriate controls are in place and are documented. The independence of the Quality Unit shall be documented and demonstrated by showing the inter-departmental relationships as well as relationship to top management.

6 Planning

6.1 Actions to address risks and opportunities

No additional requirements.

6.2 Quality objectives and planning to achieve them

The quality objectives shall:

h) include adherence to the requirements of this Annex.

6.3 Planning of changes

There shall be a documented procedure defining the responsibilities and requirements for the evaluation and approval of changes that may impact the quality of the excipient, including the impact on any regulatory submissions made by the organisation. Evaluation and approval of changes shall occur prior to implementation. The procedure shall describe how a change is determined as significant. Changes determined to be significant shall be approved by the Quality Unit and customers notified. Customer communication shall occur in advance whenever possible. Where applicable, significant changes shall also be communicated to regulatory authorities (see 8.2.1). Records of the change control process shall be retained.

The impact of changes on validated processes and activities shall be assessed. (See 8.5.1).

Note 1: For Guidance refer to the current version of the IPEC Federation Significant Change Guide for Pharmaceutical Excipients.

Note 2: Quality risk management can be utilised to evaluate proposed changes. The level of effort and formality of the evaluation should be commensurate with the level of risk.

Note 3: If changes have been discovered as being implemented without prior approval, then they should be investigated as nonconformity and the potential consequences assessed. (See 10.2).

7 Support

7.1 Resources

7.1.1 General

The organisation shall determine and provide the resources needed to meet the GMP requirements of this Annex.

7.1.2 People

No additional requirements.

7.1.3 Infrastructure

The infrastructure shall be designed, operated, cleaned, and maintained to ensure the prevention of contamination, mix-ups and unapproved use of raw materials, intermediates, and the excipient.

Where existing controls to minimise risks of excipient contamination are not considered effective, additional measures shall be documented and implemented.

Names of materials and flow directions shall be indicated on fixed pipes and lines that connect with the excipient manufacturing equipment.

The organisation shall conduct a risk assessment based on the organisation's intended use of the infrastructure to identify areas where the excipient is at risk of contamination from deficiencies in buildings and/or facilities. The risk assessment shall consider the following at a minimum to identify where the excipient is at risk from contamination:

- a) location of the operations (e.g., internal, external),
- b) state of repair of the building and facility,
- c) suitable size, construction, and location,
- d) ability to maintain a suitably clean building and facility environment, in particular to minimise the presence of dust and other foreign particulate matter.
- e) operations that can affect excipient quality,
- f) presence of airborne contaminants, especially highly sensitising or toxic substances,
- g) presence of environmental contaminants, including microorganisms.

Where existing controls to minimise risks of excipient contamination are not considered effective, additional measures shall be documented and implemented.

There shall be controls to ensure that defective equipment is not used. Equipment, including computer systems, which may impact excipient quality, shall be commissioned before initial use to ensure that it is functioning as intended.

Equipment shall be placed and constructed to facilitate cleaning and maintenance. The use, cleaning and maintenance of quality critical equipment shall be recorded. The status of equipment shall be readily identifiable. Equipment shall be constructed so that contact surfaces will not be reactive, additive, or absorptive.

As determined by the risk assessment, or where equipment cannot be cleaned to a predefined standard then dedicated equipment shall be used.

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Production processes associated with highly sensitising or toxic materials shall be separated from those used for excipients, unless measures to prevent cross-contamination have been implemented and the effectiveness of these measures has been demonstrated.

The organisation shall conduct a risk assessment considering the risk to excipient quality from utilities and process materials (e.g., nitrogen, compressed air, steam, lubricants etc.) used in the production, storage, or transfer of materials. Suitable control measures shall be implemented to mitigate identified risks.

Where immediate contact of lubricants or refrigerants cannot be avoided then the substances shall be of at least food grade quality.

Utilities in direct contact with excipients (e.g., gases) shall have a defined specification and be managed to the same standard as other raw materials (see Section 8.4).

Design qualification, installation qualification, operation qualification and performance qualification shall be conducted and documented for manufacturing buildings, facilities and equipment.

Computerised systems that may impact upon excipient quality shall have documented controls to ensure consistent operation, the integrity of data, maintenance, back-up or archiving, disaster recovery and include measures to prevent unauthorised access or changes to software, hardware, or data. Changes to computerised systems that may impact upon excipient quality shall be verified and documented. (See 6.3).

Water, where used in contact with excipients shall conform to written specifications and be monitored to confirm it is of a suitable quality for its intended use.

Note: The intended use will determine which chemical and microbiological specifications should be monitored.

Unless otherwise justified, water shall, at a minimum, meet WHO guidelines for drinking (potable) water quality.

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

Product contact water shall be produced and distributed in such a manner so as to prevent contamination entering or backflows in the system.

Where water of multiple qualities is available, provision shall be made to avoid mix-up.

When the customer has informed the organisation that the excipient is to be used in the manufacture of sterile drug products, any water in contact with the excipient during the final stages of manufacture or included in

the excipient shall be monitored and controlled for bacterial count and endotoxins.

Access to areas of buildings and facilities designated as limited access areas shall be controlled.

7.1.4 Environment for the operation of processes

The work environment shall be managed and controlled to minimise risks of excipient contamination. A documented risk assessment shall be carried out to determine the necessary controls. The risk assessment shall take into account any customer requirements and the intended use of the excipient.

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

- a) air handling systems,
- b) special environments,
- c) cleanliness and sanitary conditions,
- d) waste segregation and disposal,
- e) pest control,
- f) personnel hygiene,
- g) other risk assessments required by this Annex.

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

7.1.4.1 Air handling

Where the risk assessment has identified the need for an air handling system, it shall be designed and maintained to assure adequate protection of the excipient. The effectiveness of the system shall be demonstrated.

7.1.4.2 Controlled environment

Where the risk assessment has identified the need for a controlled environment, it shall be monitored to assure excipient quality. Where an inert atmosphere is required, the gas shall be treated as a quality critical raw material (see 8.6) or intermediate.

If interruptions in the controlled environment occur, the organisation shall perform an investigation. Evidence and appropriate rationale shall be documented to show that such interruptions have not compromised the quality of the excipient.

7.1.4.3 Cleaning and sanitary conditions

Where the risk assessment has identified the need for clean and sanitary conditions, the organisation shall document procedures assigning responsibility for cleaning and sanitation. Cleaning records shall be maintained. Waste shall be segregated and disposed of in a timely and appropriate manner. If waste is not disposed of immediately, it shall be suitably identified.

7.1.4.4 Pest control

Where the risk assessment has identified the need for pest control, the organisation shall document the pest control programme.

7.1.4.5 Personnel hygiene

Where the risk assessment has identified areas in which the excipient is at risk of contamination from personnel or their activities, the organisation shall document and consider at a minimum the following controls to prevent excipient contamination:

- a) the personnel themselves and their attire, including personal protective equipment,
- b) loose items, including those in pockets,
- c) unauthorised access to designated areas (see 7.1.3),
- d) the potential impact of any person with an apparent illness or open lesions,
- e) the storage and use of food, drink, personal medication, tobacco products or similar items.

Personnel washing facilities shall be provided, which ensure suitable hygiene standards can be maintained. Clean toilet facilities shall be separate from, but easily accessible to, working areas. Facilities for showering and/or changing clothes shall be provided, where identified in the personnel hygiene risk assessment.

Garments worn to protect the excipient from contamination shall be clean, not generate static electricity or release foreign substances.

7.1.4.6 Lighting

Adequate lighting shall be provided to facilitate cleaning, maintenance, and operations. Where the excipient is exposed to the work environment or stored, lighting shall be shatter-proof or otherwise protected.

Adequate lighting shall be provided to facilitate cleaning, maintenance, and operations. Emergency lighting shall be installed in accordance with the relevant regulations. Where the excipient is exposed to the work environment or stored, all lighting shall be shatter-proof or otherwise protected.

7.1.4.7 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 brake or other mechanical device to prevent back-siphoning.

7.1.5 Monitoring and measuring resources

7.1.5.1 General

No additional requirements.

7.1.5.2 Measurement traceability

No additional requirements.

7.1.6 Organisational knowledge

The organisation shall have knowledge of the regulations concerning the use of the excipients supplied.

Note: Knowledge would be aligned to the claims made about excipient,

Annex to ISO 9001:2015: Additional requirements for GMP for Pharmaceutical Excipients its intended uses, and the countries in which it is marketed.

7.2 Competence

Personnel whose role has an impact on excipient quality shall have written job descriptions.

Consultants advising on the design, production, packaging, testing, distribution, or storage of excipients shall have sufficient education, training and experience or any combination thereof to advise on the subject for which they are retained. Records shall be maintained listing the name, address and qualifications of consultants providing advice concerning any aspect of the Quality Management System and the type of service they provide.

The organisation shall:

- e) ensure training, including the requirements of this Annex as it relates to the employee's function, is conducted by qualified individuals,
- f) ensure training is conducted prior to carrying out the assigned duties,
- g) ensure training includes:
 - i. GMP principles and the contents of this Annex,
 - ii. the risk of contamination to excipient quality,
 - iii. the potential hazard to end user/patient if an excipient is contaminated,
 - iv. potential impact on excipient quality and use, due to departures from specified procedures,
 - v. the risk of excipient contamination from deficiencies in personal hygiene,
 - vi. the reporting of significant failures and deviations from procedures.
- h) ensure GMP refresher training is conducted with sufficient frequency such that employees remain familiar with applicable elements of this Annex.

7.3 Awareness

The organisation shall ensure that persons doing work under the organisation's control are aware of:

- f) the point from which processes must
- g) be performed under the GMP requirements defined by this Annex,
- f) the consequences of contamination.

7.4 Communication

GMP and regulatory requirements shall be communicated as appropriate throughout the organisation.

Top management shall be promptly notified about any quality critical situations (for example those that would lead to a product recall from the

Annex to ISO 9001:2015: Additional requirements for GMP for Pharmaceutical Excipients market), in accordance with a documented procedure.

7.5 Documented information

7.5.1 General

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

The organisation's quality management system shall include:

- c) the organisation's overall intentions and approach to GMP,
- d) procedures required for conformance to this Annex including the controls needed for documented information (see 7.5.3),
- e) a documented risk assessment that defines and justifies when the "as applicable" clauses in this Annex are not implemented.

7.5.2 Creating and updating

Documents that impact product quality shall have a defined owner.

The Quality Unit shall review and approve documents that impact product quality, including changes to these documents.

Note: The Quality Unit may delegate this activity, unless otherwise noted herein, if appropriate controls are in place and are documented. (See 5.3).

Electronic documentation shall meet the requirements stated above.

If electronic signatures are used on documents, they shall be controlled to be as secure as a hand-written signature.

Note: Electronic documents and signatures may also need to satisfy local regulatory requirements.

The organisation shall define which records, results and reports of subcontractor activities shall be retained and by whom.

Electronic records shall be subject to the same controls as those required for other records.

Entries in quality records shall be clear, indelible, and made directly after performing the activity (in the order performed), signed or initialled and dated by the person making the entry. Corrections to entries shall be signed or initialled and dated, leaving the original entry legible.

7.5.3 Control of documented information

7.5.3.1

Documented information required by the quality management system and by this International Standard shall be controlled to ensure:

- c) designated personnel approve documents for adequacy prior to issue,
- d) they are periodically reviewed, updated as necessary and re-approved,
- e) obsolete documented information is prevented from unintended use,
- f) suitable identification is applied if they are retained for any purpose.

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g) that documents and records are traceable and in the case of records they are unique.

The record retention period shall not be less than one year past the excipient's expiry or last re-evaluation date or shall be at least five years from the date of manufacture.

Certificates of Analysis (CoAs) and Certificates of Conformity (CoCs) are records that are required to ensure product traceability back to the manufacturer. Documented procedures shall be implemented to ensure control of Certificates.

7.5.3.2

No Additional requirements.

8 Operation

8.1 Operational planning and control

The organisation shall plan, implement, and control the processes (see 4.4) needed to meet the requirements for the provision of products and services, and to implement the actions determined in Clause 6, by:

- f) documenting testing programmes for quality critical materials, intermediates and excipients that include appropriate specifications, sampling plans, test and release procedures,
- g) implementing environmental and hygiene control programmes as identified in 7.1.4 to minimise risks of contamination of the excipient,
- h) documenting procedures describing activities relating to the storage and distribution of excipients,
- i) implementing identified actions from risk assessments described in other sections of this Annex.
- j) manage the identification, storage, subculture and screening of biological organisms used in the manufacture of excipients.

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

8.2 Requirements for products and services

8.2.1 Customer communication

Communication with customers shall include:

- f) notification of significant changes. (See also 6.3 and 8.2.2),
- g) notification of critical deviations which become known after delivery of the excipient. (See 8.2.2, 8.2.3 and 8.2.4),
- h) notification of a product recall.

Certificates of Analysis, which are traceable to the original manufacturer's CoA, shall be provided for each batch shipped.

Where the excipient is not manufactured by the supplier, the original manufacturer's identity and production site shall be communicated to the customer.

The organisation shall establish a system for releasing EXCiPACT audit reports to customers including any action plans agreed with the Certification Bodies.

8.2.2 Determination of requirements for products and services

When determining the requirements for the products and services to be offered to customers, the organization shall ensure that:

a) the requirements for products and services are defined, including:

1) any applicable statutory and regulatory requirements.

The organisation shall document these requirements and demonstrate how they comply with them. Any registrations or licences they hold therefore shall be kept up to date.

Note: Regarding ISO 9001:2015 8.2.2 a), i), statutory and regulatory requirements can include for example, compendial general requirements, including TSE/BSE, residual solvents, elemental impurities.

8.2.3 Review of the requirements for products and services

No additional requirements.

8.2.4 Changes to requirements for products and services

Changes requiring notification and/or documented prior approval from the customer shall be defined.

Note: Regarding ISO 9001:2015 8.2.2 a), i), statutory and regulatory

Annex to ISO 9001:2015: Additional requirements for GMP for Pharmaceutical Excipients requirements can include for example, compendial general requirements, including TSE/BSE, residual solvents, elemental impurities.

8.3 Design and development of products and services

The extent of conformance to this Annex for development batches of excipients shall be communicated to the customer. (See 8.2.1).

8.3.1 General

No additional requirements.

8.3.2 Design and development planning

No additional requirements.

8.3.3 Design and development inputs

No additional requirements.

8.3.4 Design and development controls

No additional requirements.

8.3.5 Design and development outputs

No additional requirements.

8.3.6 Design and development changes

No additional requirements.

8.4 Control of externally provided processes, products, and services

8.4.1 General

Quality critical materials and services shall be identified and justified.

Note: Risk assessment techniques are a useful way of identifying quality

Suppliers of quality critical materials and services shall be approved by the Quality Unit after a documented evaluation of the supplier's quality management system, including adequate evidence that they can consistently meet agreed requirements.

The organisation shall require that contract manufacturers or laboratories adhere to the relevant sections of this Annex. (See 4.4).

Primary packaging material specifications shall be established, and a written procedure shall clearly define primary packaging materials for each individual excipient based upon the excipient's properties and stability.

8.4.2 Type and extent of control

The organisation shall:

- e) define the responsibility for quality and the control measures within the quality management system,
- f) communicate the applicable GMP principles in accordance with this Annex which are to be applied to those operations.

Incoming quality critical materials shall be physically or administratively quarantined until they have been tested or otherwise verified and approved for use. Where quarantine is not feasible, e.g., for materials supplied via pipelines, the excipient manufacturer shall establish an agreement with the supplier so that they are notified of material that does not meet specification.

Animal Health certificates and other related documents (e.g., Phytosanitary Certificates) shall be provided and retained for incoming materials of animal or vegetable origin.

The organisation shall define and document the controls used to verify the identity and quality of purchased product.

Sampling shall be conducted in accordance with a documented procedure designed to prevent contamination.

Quality critical materials used in the manufacture of the excipient shall be tested or otherwise verified before use. Materials which are not sampled shall have alternative controls in place to assure their quality.

Bulk deliveries shall have controls to ensure freedom from contamination.

8.4.3 Information for external providers

The organisation shall communicate to external providers its requirements for:

- g) notification of subcontracting or other significant changes to materials that may potentially impact excipient quality.

8.5 Production and service provision

8.5.1 Control of production and service provision

Controlled conditions shall include, as applicable:

a) *The availability of documented information that defines,*

3) Work instructions and records for batch and continuous processes.

Records shall be retained for each batch of excipient produced and shall include information relating to the production and control of the batch. The organization shall define a batch of excipient (See Appendix for definition). Where critical to excipient quality, records shall include:

- date/time each step was completed or date/time log of key parameters,
- identification of persons performing or checking each operation or control parameter,
- identification of major equipment and lines used,
- cleaning of equipment and utensils,
- conformance to specified operating ranges,
- material inputs to enable traceability (for example, batch number and quantities of raw material/intermediate, time it was added, etc.), and to verify the intended quantity has been added,
- description of sampling performed,
- in process and laboratory control results,
- labelling control records,
- failures, deviation, and their investigations,
- results of final product inspection.

- | |
|--|
| <ul style="list-style-type: none">• the target durations for critical steps in the manufacturing process |
|--|

And as applicable:

- the quantity produced in quality critical steps and the final batch and a statement of the percentage of theoretical yield,
- in cases where it is not be possible to exactly add the defined quantity for technical reasons, a defined range around the target quantity should be defined.
- verification of the homogeneity of mixed batches.

Records of quality critical equipment use shall allow the sequence of cleaning, maintenance, and production activities to be determined. Where multi-purpose equipment is in use records shall identify the previous usage.

Packaging and labelling controls shall be documented and shall ensure:

- packaging and labelling facilities are inspected immediately before use to ensure that materials that are not required for the current operation have been removed,
- correct labels are printed and issued containing the correct information,

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- the information on the label shall be indelible,
- the correct label is applied to all containers,

- excess labels are immediately destroyed or returned to controlled storage.

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

Where heating or irradiation is used post manufacture to reduce microbiological contamination of the excipient, the treatment shall be operated within the limits proven to be effective. post manufacturing treatments shall not be routinely used as a substitute for poor microbiological controls during manufacture.

- b) *The availability and use of suitable monitoring and measuring resources,*

No additional requirements.

- c) *The implementation of monitoring and measuring activities....,*

Sampling methods shall be documented and shall define the time and location of sampling and shall ensure that the sample is representative and clearly labelled. In-process samples shall not be returned to production for incorporation into the final batch.

- d) *The use of suitable infrastructure and environment for the operation of processes,*

The organisation shall design and justify equipment cleaning and sanitisation procedures and provide evidence of their effectiveness.

Where equipment is held in an unused state before or after cleaning, the maximum hold periods should be defined. These hold periods shall be recorded and evaluated as part of batch release (See Section 8.6).

Note: Cleaning effectiveness may be compromised if used equipment remains in that condition for a protracted period. A risk assessment may help define maximum hold periods.

Equipment and utensils shall be cleaned, and where critical to excipient quality sanitised. The cleaning/sanitisation status of equipment shall be identified.

For dedicated equipment, the frequency of equipment cleaning shall be determined by the organisation and justified.

- e) *The appointment of competent persons, including any required qualifications,*

No additional requirements.

- f) *The validation and periodic revalidation of the ability to achieve planned results of the process for production and service provision, where the resulting output cannot be verified by subsequent monitoring and measurement,*

A validation plan shall be defined for all equipment, infrastructure, cleaning, methods and related activities that have a direct impact on excipient quality. Individual validation protocols shall be prepared stating the examinations to be performed and their acceptance criteria. A validation report shall be approved by the Quality Unit.

Note: A risk assessment may be used to develop the validation protocols.

The organization shall define how they will conduct Process Validation.

Note: Effective control of the manufacturing process may be demonstrated by statistical methods.

Process validation shall be conducted to define and demonstrate effective control of the manufacturing process including sampling and in-process testing activities. Re-validation of the process shall be conducted where evaluation of changes (see Section 6.3) identifies there is an impact on excipient quality.

The consistent operation of the excipient manufacturing process shall be demonstrated based on knowledge of process parameters, product attributes and their inter-relationship.

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.

After implementation of significant changes, the impact on process capability shall be assessed.

g) *The implementation of actions to prevent human error,*

No additional requirements.

h) *The implementation of release, delivery, and post-delivery activities.*

No additional requirements.

8.5.2 Identification and traceability

Identification and traceability are necessary requirements for quality critical raw materials, packaging materials, intermediates, and finished excipients. Storage containers shall be identified and marked with their contents.

Records shall allow traceability of the excipient from raw materials through delivery to initial customers. The methods used for traceability and identification of raw materials used in excipients produced by continuous processing shall be defined.

The organisation shall ensure there is a process to communicate the origin and traceability of the excipient to the customer.

Excipient labels shall include as a minimum:

- a) the name of the excipient and grade if applicable,
- b) the organisation's name and address,
- c) the batch number,
- d) any special storage conditions, if applicable.

Delivery records to initial customers shall include sufficient information to allow the specific batch to be traced and retrieved if necessary.

8.5.3 Property belonging to customers or external providers

No additional requirements.

8.5.4 Preservation

Storage conditions shall be maintained. They shall be monitored and recorded if they are critical for the maintenance of packaging, raw material, intermediate or excipient quality characteristics. Deviations from specified storage conditions shall be assessed. Storage and handling procedures shall be defined to protect containers, labels, and closures, minimise the risk of contamination, damage or deterioration of the excipient, and prevent mix ups.

There shall be a system in place to ensure that the excipient will be supplied within its expiry and/or retest interval.

Suppliers of transport services shall be provided with the required transport-controlled conditions for them to maintain required conditions.

For bulk transport verified cleaning procedures shall be justified and applied. Records of cleaning shall be retained.

A list of restricted and/or allowed previous cargoes shall be supplied to the transport companies.

Steps shall be taken, such as tamper evident seals, to provide evidence of unauthorised access to the materials being transported.

The selection of excipient packaging systems shall be justified and documented by the organisation. An excipient packaging system shall include the following features:

- a) written packaging specifications, including any special storage conditions required to preserve the packaging,
- b) containers that do not interact with or contaminate the excipient,
- c) tamper evident seals, unless written justification demonstrates these are not feasible to apply,
- d) where containers are to be re-used for the excipient, verified cleaning procedures including means of removing previous labels shall be applied. Records of cleaning shall be retained.

Note: A tamper evident seal should have a distinct design and possess

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unique identifying characteristics that are difficult to duplicate. Each tamper evident seal should be traceable to and, where feasible, accounted for by the excipient manufacturer and should not be reusable once the seal is broken.

8.5.5 Post-delivery activities

No additional requirements.

8.5.6 Control of changes

See Section 6.3.

8.6 Release of products and services

Test methods shall be documented and suitable for their intended purpose.

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

- non-compendial analytical tests shall be demonstrated to be at least equivalent to those in the compendia,
- the method shall comply with applicable general chapters and notices,
- the responsibility for monitoring the current pharmacopoeia or official compendium shall be assigned.

Written procedures shall be established to monitor and control the quality characteristics of excipients. These shall include, as applicable:

- a) laboratory controls: including the preparation and use of laboratory solutions, reference standards,
 - i. laboratory controls shall include complete data derived from tests necessary to ensure conformance with specifications and standards. Records of these controls shall include:
 - ❖ identification and traceability of samples,
 - ❖ test method used,
 - ❖ raw data including sample preparation,
 - ❖ calculations performed,
 - ❖ test results and how they compare with established specifications,
 - ❖ name of the person who performed each test and the date(s) the tests were performed.
 - ii. there shall be a documented procedure and records for the preparation of laboratory reagents and solutions. Reagents and solutions shall be labelled with the name, concentration, and expiry date,
 - iii. primary reference standards and purchased reagents shall be verified on receipt and appropriately stored. There shall be a documented procedure for the qualification of secondary reference standards against primary reference standards that includes their

Annex to ISO 9001:2015: Additional requirements for GMP for Pharmaceutical Excipients preparation, approval, and storage. The re-evaluation period shall be defined for secondary reference standards and each batch shall be periodically re-qualified in accordance with a documented procedure.

b) excipient testing and release,

- i. there shall be a procedure to ensure that appropriate manufacturing documentation, in addition to the conformance of test results to specifications is evaluated prior to release of the finished excipient. The Quality Unit shall be responsible for the release of the finished excipient. (See 5.3).

Note: For excipients produced by a continuous process, assurance that the excipient conforms to documented specifications may be achieved through the results of in-process testing or other process monitoring measures.

c) investigation of out-of-specification test results,

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

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

- a. statistical techniques that are to be used and under what circumstances,
- b. criteria for the use of retest and/or resample results,
- c. criteria for resampling.

d. the records and the justification for the release of an affected batch

- d) the retention of samples of each batch of the excipient,
- i. a representative sample of each batch of the excipient shall be retained, unless otherwise justified and documented,
 - ii. for packaged excipients, the retention period shall be justified and based on the excipient's expiry or re-evaluation date,
 - iii. for bulk excipients, the retention period shall be justified and based on the expiry or re-evaluation interval, or the duration of the shipment to the customer,
 - iv. shall be stored in a secured location, readily retrievable and in conditions consistent with the recommended storage conditions for the finished excipient,
 - v. the sample size shall be at least twice the amount required to perform complete specification testing.
- e) preparation and issue of certificates of analysis, The Certificate of Analysis shall include as a minimum⁴ :
- the excipient name and, if applicable, grade and compendial reference,
 - the manufacturer's name and site of manufacture,
 - the date of manufacture,
 - the lot or batch number,
 - the expiration, retest, or re-evaluation date,
 - a statement of compliance to the required specification,
 - the analytical results specific to the lot or batch, unless otherwise noted and explained,
 - the acceptance criteria,
 - the analytical method reference,
 - the identity of the authorised individual who approved the Certificate of Analysis.
- f) the tests and limits for impurities,
- i. excipient manufacturers shall identify and set appropriate limits for known impurities and known objectionable microorganisms.

Note: The limits should be based upon appropriate safety data or limits as described in official guides and compendia (e.g., residual solvents and metal catalysts).

- g) an evaluation of excipient stability.

⁴ See also the IPEC Certificate of Analysis Guide for pharmaceutical excipients.

- i. the organisation shall evaluate excipient stability based on historic data or specific studies. The organisation shall define and justify an expiry or retest interval and ensure this is communicated to the customer.

ii. the organisation shall define a stability testing programme which includes

- the number of lots to be tested each year,
- the storage conditions,
- the storage containers (which should simulate the final packaging where possible)
- the sampling intervals,
- the stability indicating test methods

The Organisation shall implement the stability testing programme where there is insufficient historic data to support the assigned retest or expiry interval or when there are significant changes to the manufacturing process.

Note: For excipients with sufficient data to support the assigned retest or expiry interval then periodic testing may not be conducted every year.

8.7 Control of nonconforming outputs

8.7.1

Blending of contaminated or adulterated batches to reduce the contamination or adulteration below an acceptable or detectable limit is not acceptable under this Annex.

The organisation shall deal with nonconforming outputs in one or more of the following ways:

- e) reprocessing shall only occur when it has been assessed that the excipient may be processed in that manner,
- f) reworking shall only occur after the Quality Unit has documented a risk assessment; consideration shall be given to:
- new impurities that may be introduced because of reworking,
 - additional testing to control the reworking,
 - records and traceability to the original batches,
 - suitable acceptance criteria for the reworked excipient,
 - impact on stability or the validity of the re-evaluation interval,
 - impact on the performance of the excipient.

The method of reworking shall be documented and in compliance with the outputs of the risk assessment.

Incidences of non-conformance shall be investigated

- to assess the impact on other batches/products and on validated

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- to identify the root causes and define actions for improvement (see Section 10.2).

There shall be a documented procedure defining how to manage excipient recall. The regulatory authorities that require notification of a recall shall be identified. All recall processes shall be documented, notified to the original manufacturer, regulatory authorities as identified, and records retained. Recalled materials shall be identified and quarantined.

Note:

In the USA, the term 'recall' has specific regulatory implications, and it is more common to use the term 'retrieval' for the procedure described above (See glossary under recall).

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 conformance of a returned excipient has been confirmed and the intent is to make the returned excipient available for sale to another pharmaceutical customer, the evaluation shall consider its integrity and conformance to the required storage and/or transportation conditions throughout the supply chain. Records shall ensure traceability, include the reason for return and the decision made as to the new disposition.

8.7.2

Records of reprocessing and reworking activities shall be retained.

9 Performance Evaluation

9.1 Monitoring, measurement, analysis, and evaluation

9.1.1 General

No additional requirements.

9.1.2 Customer satisfaction

No additional requirements.

9.1.3 Analysis and evaluation

No additional requirements.

9.2 Internal

Audit 9.2.1

The organisation shall conduct internal audits at planned intervals to determine whether the quality management system.

c) conforms to the requirements of this Annex.

9.2.2.

No additional requirements.

9.3 Management Review

9.3.1 General

No additional requirements.

9.3.2 Management review input

The management review shall be planned and carried out taking into consideration:

- g) new, revised or proposed regulatory requirements,
- h) the suitability of the quality policy. (See 5.3),

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| i) a summary of trends concerning excipient quality attributes, customer complaints and manufacturing capability. |
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j)

9.3.3 Management review output

The outputs of the management review shall include decisions and actions related to:

- d) improvements necessary because of the review of regulatory requirements,
- e) any need to update the quality policy.

Note: Necessary changes identified in the management reviews should be assessed and implemented via the change control procedure. (See 6.3).

10 Improvement

10.1 General

No additional requirements.

10.2 Nonconformity and corrective action

No additional requirements.

10.3 Continual improvement

No additional requirements.

Definitions (remainder to be added)

Batch (lot): A specific quantity of material produced in process or a series of processes so that it can be expected to be homogenous. In the case of a continuous process, a batch may correspond to a defined fraction of the production. The batch size can be defined by a fixed quantity or by the amount produced in a fixed time interval. [IPEC]
ANSI NSF reworded to 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.