Certification Standards for Pharmaceutical Excipient Suppliers

Good Manufacturing Practices (GMP)
Good Distribution Practices (GDP)
Good Warehousing Practices (GWP)

Requirements for Auditor Competency and Third-Party Organisations Providing Certification of the Management System

2021

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Note: New content is in orange font

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Dedication

This document is dedicated to the memory of Dr Arnulf Heubner who until his untimely death in November 2009 was Senior Director Pharma Raw Materials, Performance and Life Science Chemicals at Merck KGaA, Darmstadt, Germany, a founder member of the EXCiPACT project, a Board Member of the European Fine Chemicals Group (EFCG) and Chairman of their Pharmaceuticals Business Committee. His knowledge, wisdom and enthusiasm are greatly missed.

Acknowledgements

EXCiPACT asbl is the result of a huge amount of effort and commitment from a team of people spanning two continents and many countries. These individuals are members of the partner organisations that comprise EXCiPACT asbl and without whom these standards and requirements could not have been prepared.

Federation of European Chemical Distributors (FECC)

The European Association of Chemical Distributors (FECC) is the European voice of the chemical distribution industry. With a growing membership of companies and national associations, FECC represents over 1200 entities many of which are small and medium sized enterprises. Members service a very wide range of industries and meet the distribution requirements of sectors as diverse as electronics, paints and textiles to cosmetics food, feed, and pharmaceuticals, each with their own diverse demands and purchase volumes.

For further information visit www.fecc.org

International Pharmaceutical Excipients Council (IPEC Federation)

IPEC is an international industry association formed in 1991 by manufacturers and end-users of excipients. It is an association comprising four regional pharmaceutical excipient industry associations covering the United States, Europe, China and Japan (which are known respectively as IPEC-Americas, IPEC Europe, IPEC China, IPEC India and IPEC Japan). IPEC's objective is to contribute to the development and harmonisation of international excipient standards, the introduction of useful new excipients to the marketplace and the development of good manufacturing and distribution practice for excipients.

IPEC first published its GMP Guide for Bulk Pharmaceutical Excipients in 1995 and it was revised in 2001 to align it with ISO 9001:2000 and again in 2006 to bring it fully up to date. This document has also been adopted by the USP and has been published as general chapter <1078> with only minor editorial changes to make it suitable for that publication. Collaboration with PQG led to the established and widely accepted IPEC/PQG Good Manufacturing Practices Guide for Pharmaceutical Excipients, 2006. IPEC also published the Good Distribution Practices Guide for Pharmaceutical Excipients in 2006.

For further information visit www.ipec.org

Pharmaceutical Quality Group (PQG)

The PQG was formed in 1977 to promote development of a consistent approach to pharmaceutical quality and good manufacturing practice. PQG

provides support to the pharmaceutical industry and its suppliers with training, discussion meetings and certification standards and guidance. In 1990 the PQG published three codes of practice to cover pharmaceutical raw materials, printed and contact packaging materials. In 1995 the codes were revised and were integrated with ISO 9002:1994. The code for raw materials was revised and reissued as PS 9100:2002 Pharmaceutical excipients, an application standard and GMP guide for pharmaceutical excipients. Collaboration with IPEC led to the established and widely accepted IPEC/PQG Good Manufacturing Practices Guide for Pharmaceutical Excipients, 2006.

For further information visit www.pqg.org

2021 Standards Revision (in orange font throughout)

The following individuals from the member organisations involved in the delivery of the EXCiPACT Certification Scheme contributed to the design and development of the Good Warehousing Practice Annex for closed pack excipients.

EXCiPACT asbl thanks the following individuals for their time, expertise, and skill in drafting this annex.

Mathias Brenken	IPEC Europe	MB-QAR
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The contributions of the many reviewers who provided comments on the draft GWP Annex are also acknowledged with thanks.

Other amendments throughout the rest of the standards were made following constructive feedback from all stakeholders and through operation of the EXCiPACT Certification Scheme.

General Introduction

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 system[1].

This 2017 edition of the EXCiPACT Standards publication has been comprehensively updated to align with recent changes in the ISO 9001 and ISO/IEC 17021 Standards as well as NSF/IPEC/ANSI 363-2016 US National Standard Good Manufacturing Practices (GMP) for Pharmaceutical Excipients.

Changes from the 2nd Edition 2017

Some corrections were made to align the GMP and GDP sections to make identical the requirements for the same subject matter.

A new Annex for additional Requirements for Applying GDP to original, closed-pack Pharmaceutical Excipients ("GWP") has been added. This is effectively a sub-set of the GDP requirements for this specific scenario and to keep the text simple any reference to GDP may also refer to the GWP annex as the context permits.

Several clauses in the ISO 17021-1 annex have been clarified and the actions to be taken when suspending or even withdrawing a certificate have been made clearer.

Remote audits have been allowed if conducted in accordance with the EXCiPACT instructions published on the website, which were necessary to accommodate the societal changes brought about by the COVID-19 pandemic.

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.

These tragedies have taught us that it is not sufficient to only apply the principles of Good Manufacturing Practice (GMP) to the manufacture of the excipient but also that Good Distribution Practice principles (GDP) must be applied by all organisations involved in excipient distribution. Excipient quality can be better assured if all steps in the supply chain, from

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

manufacturer through to user, adopt suitable standards that are capable of independent verification.

Legislators and regulatory authorities in both Europe and the USA have addressed and continue to address the weaknesses in the application of GMP and GDP to pharmaceutical excipients to minimise patient risk. A common theme in these regulatory requirements is that the excipient user has to have knowledge of the management systems and GMP used to manufacture and/or the GDP used to distribute the excipient. As a result, excipient supplier sites could be asked to host hundreds of extra audits. In recognition of these issues the authorities have clearly stated that the excipient user (drug product manufacturer) can utilise third party audit organisations to perform the audits[2]. 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 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 this certification scheme for excipient suppliers – EXCiPACT Certification Scheme for excipient suppliers which was launched in 2012. The GMP and GDP standards used for certification were based on the widely accepted IPEC-PQG GMP and the IPEC GDP Guides 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 these EXCiPACT GMP GDP and GWP standards as three annexes to ISO 9001:2015. This allows excipient suppliers to be assessed to ISO

[2] 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).

9001:2015 and the EXCiPACT GMP or GDP or GWP annex at the same time.

Those suppliers which do not hold ISO 9001 certification will find the US National Standard (Good Manufacturing Practices (GMP) for Pharmaceutical Excipients NSF/IPEC/ANSI 363-2016) is an alternative approach: this standard is also based on the original IPEC-PQG GMP Guide 2006. With this edition of the EXCiPACT GMP, GDP and GWP standards, the current editions of the IPEC-PQG GMP Guide, the IPEC GDP Guide and NSF/IPEC/ANSI 363 are fully aligned.

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. Originally the auditor competency requirements were based on ISO 19011:2002, Guidelines for Quality and/or Environmental Management System Auditing, and the quality management system requirements were based on ISO/IEC 17021:2006, Conformity assessment - Requirements for Bodies Providing Audit and Certification of Management Systems. However, ISO updated the ISO/IEC 17021 standard in 2012 (just as EXCiPACT was launched) and included auditor competency requirements in the revision. In 2015 the standard was again revised becoming ISO/IEC 17021-1:2015. As a result, the original two EXCiPACT annexes on auditor competency and quality management system requirements for Certification Bodies have been consolidated into one annex, aligned to the current ISO/IEC 17021-1:2015. Again, no new requirements have been included as a result of this revision.

Despite all the changes in the alignment of the clauses in the standards throughout there are very few new requirements. For the most part, any changes have been the result of feedback from the first 8 years of use of the standards and to make the intent of each clause clearer.

EXCiPACT

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

Revision 2021

Foreword to the ISO 9001 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.

0.1 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.

0.2 Quality Management principles

No additional requirements.

0.3 Process approach

0.3.1 General

No additional requirements.

0.3.2 Plan-Do-Check-Act cycle

No additional requirements.

0.3.3 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.

0.4 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, 2011[3].

Note: See also Appendix 2 for other references.

[3] http://www.who.int/water_sanitation_health/publications/2011/dwq_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

No additional requirements.

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:

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

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 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 organisation.

Top management shall assign the authority and responsibility for:

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

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 avoid contamination and mix-ups of raw materials, intermediates, and the excipient.

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,
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.

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.

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.

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.

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.

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, 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 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.

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.

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 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 critical materials and services.

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.

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. 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.),
- description of sampling performed,
- in process and laboratory control results,
- labelling control records,
- failures, deviation, and their investigations,
- results of final product inspection.

And as applicable:

- the quantity produced for the defined batch and a statement of the percentage of theoretical yield,
- 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,
- 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.

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.

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,*

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.

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 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 organisation 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 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 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 minimum[4] :
   - 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.

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 processes and activities (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).

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.

EXCiPACT

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

Revision 2021

Foreword to the ISO 9001 GDP Annex

Many excipient manufacturers and distributors are already registered to ISO 9001:2015, "Quality Management Systems – Requirements", and as a consequence 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 GDP for pharmaceutical excipients. This Annex to ISO 9001:2015 is based on the current version of the IPEC Good Distribution 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 distribute excipients can choose to be certified to this Annex and the corresponding GMP 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 GDP requirements:

Texts in Bold are ISO 9001:2015 Headings
Standard Texts are GDP 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 GDP annex is based on a re-alignment of the clauses in the EXCiPACT GDP 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 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 these standards 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.

0.1 General

Excipient distribution shall be carried out in accordance with Good Distribution Practice (GDP) principles consistent with this Annex. The objective of excipient GDP is to ensure that the distribution 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 assure that appropriate records are maintained.

Throughout this document, references to "GDP for pharmaceutical excipients" will be referred to as "GDP" 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 GDP to the distribution 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.

0.2 Quality Management principles

No additional requirements.

0.3 Process approach

0.3.1 General

No additional requirements.

0.3.2 Plan-Do-Check-Act cycle

No additional requirements.

0.3.3 Risk-based thinking

The manufacture, origin and distribution of excipients is exceptionally variable, therefore a "one size fits all" approach to the definition of excipient GDP is not possible. In such circumstances, utilising risk assessments by the excipient distributor will identify those aspects of distribution that require the implementation of GDP controls to minimise the threats to excipient quality, patient safety and regulatory compliance. Therefore, widespread use is made in this Annex for the excipient distributor 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 distributor may utilise those best suited to their circumstances.

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

0.4 Relationship with other Management System standards

No additional requirements.

Quality Management and GDP systems – requirements

1 Scope

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

Note: The requirements of this Annex are not sufficient for the distribution 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 Good Distribution Practices Guide for Pharmaceutical Excipients.

2 Normative References

ISO 9001:2015 Quality Management Systems - Requirements
WHO, Guidelines for Drinking-water Quality, 4th edition, 2011[5]

Note: See also Appendix 2 for other references.

[5] http://www.who.int/water_sanitation_health/publications/2011/dwq_guidelines/en/

3 Terms and Definitions

See Appendix 1 "Definitions".

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

No additional requirements.

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 GDP for the distribution 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 distribution process for each excipient within scope. (See Section 1).

Note: The GDP principles in this Annex may be applied earlier than this point in the excipient distribution 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:

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

Where 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 GDP principles in accordance with this Annex are applied to those operations.

Note: Quality risk management can be useful for identifying and 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 GDP 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 GDP 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 GDP 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 organisation.

Top management shall assign the authority and responsibility for:

f) an independent Quality Unit shall be responsible at a minimum for:
   - ensuring quality critical activities are identified and undertaken as defined,
   - approving suppliers of quality critical materials and services,
   - approving or rejecting packaging components and finished excipients,
   - reviewing batch records to ensure that significant deviations have been fully investigated and documented,
   - 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,
   - developing and implementing an internal audit programme,
   - ensuring that providers of outsourced services have agreed to comply with the relevant sections of this Annex.

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 excipient quality, 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 GDP 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 avoid contamination and mix-ups of the excipient.

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,
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.

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 processing, storage, or transfer of materials. Suitable control measures shall be implemented to mitigate identified risks.

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.

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.

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.

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 break 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, 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 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. GDP 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. the 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 GDP 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:

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

7.4 Communication

GDP 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 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 GDP,
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.

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, 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.

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,
i) the transfer of quality or regulatory information, from the original manufacturer of the excipient to the customer.

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

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.

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 re 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 consequently 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 requirements can include for example, compendial general requirements, including TSE/BSE, residual solvents, elemental impurities.

8.3 Design and Development of products and services

No additional requirements.

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

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

g) the responsibility for quality and the control measures within the quality management system,
h) the applicable GDP principles in accordance with this Annex which are to be applied to those operations.

Quality critical materials and services shall be identified and justified.

Note: Risk assessment techniques are a useful way of identifying quality critical materials and services.

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 available. When the excipient is repacked, 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.

Where manufacturing, testing or other operations that could affect excipient quality are outsourced the organisation shall demonstrate that the applicable GDP principles in accordance with this Annex are applied to those operations.

Incoming quality critical materials (including pre-printed labels) shall be physically or administratively quarantined until they have been tested or otherwise verified and approved for use. Where quarantine is not feasible, the excipient distributor shall establish an agreement with the supplier so that they are notified of material that does not meet specification.

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.

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,*

1) For re-packaging written instructions shall be made available to the operator.

Records shall be retained for each batch of excipient repacked and shall include information relating to the production and control of the batch.

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 material, time it was added, etc.),
- description of sampling performed,
- in process and laboratory control results,
- labelling control records,
- failures, deviation, and their investigations,
- results of final product inspection.

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,
- 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.

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.

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

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,*

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.

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

The original manufacturer, intermediaries and handling operations of the excipient shall be traceable. The identity of the original manufacturer shall be made available to customers.

Storage containers shall be identified and marked with their contents.

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.

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, 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.

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

Written packaging specifications, including any special storage conditions required to preserve the packaging,

a) containers that do not interact with or contaminate the excipient,

b) tamper evident seals, unless written justification demonstrates these are not feasible to apply,

c) 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 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 organisation 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 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 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).

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 retention of samples of each batch of the excipient,
   i. when repackaged, 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 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 minimum[6]:
   - the excipient name and, if applicable, grade and compendial reference,
   - the distributor's name,
   - the date of manufacture,

[6] See also the IPEC Certificate of Analysis Guide for pharmaceutical excipients

- 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.

The original manufacturers name and address shall be communicated to the customer.

f. an evaluation of excipient stability.

i. where excipients are repackaged, there shall be documented evidence that their stability has not been adversely affected and specified expiry dates or retest intervals are justified.

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:

g) rejection,

h) downgrading to a grade of lower quality,

i) return of the material to the original manufacturer,

j) disposal.

There shall be procedures for the holding, testing, and downgrading of nonconforming excipient.

Incidences of non-conformance shall be investigated to assess the impact on other batches/products and on validated processes and activities (see Section 10.2).

Customer complaints and information about possible defects shall be systematically investigated and documented, based on a written procedure with assigned responsibilities.

There shall be a documented procedure defining how to manage excipient recall. 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 applicable, 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

No additional requirements.

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

f) 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).

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.

EXCiPACT

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

Revision 2021

Foreword to this annex

There are many organisations involved in the excipient supply chain including warehouses that receive, store and despatch excipients in the original packs as received without any changes to the packs or labels. Where these organisations are already registered to ISO 9001:2015, "Quality Management Systems – Requirements", they can be assessed simultaneously to ISO 9001:2015 and to the requirements herein. This Annex to ISO 9001:2015 is based on that part of the current version of the EXCiPACT Good Distribution Practices (GDP) Annex for Pharmaceutical Excipients which applies to storage, warehousing, and transportation of packed excipients. Throughout this Annex the term Good Warehousing Practices (GWP) refers to the good practices associated with the receipt, storage, despatch, and transportation of pharmaceutical excipients in the original containers, and which are not relabelled.

Note: The scope of this Annex is fully aligned with the IPEC Federation GDP Guide Matrix of Applicability columns entitled "Warehousing / Distribution".
The main text that follows is based on the headings in ISO 9001:2015 and details pharmaceutical excipient GWP requirements.

Texts in Bold are ISO 9001:2015 Headings

Standard Texts are GWP 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.

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 receipt, storage, despatch, and transportation of excipient products. For organisations 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. The objective of certification to these standards is to reduce the number of these audits for users. EXCiPACT certification might not always be sufficient for every customer's supplier qualification requirements, so audits of suppliers of excipients may still be required.

0.1 General

Excipient storage shall be carried out in accordance with GWP principles consistent with this Annex. The objective of excipient GWP is to ensure that:

- the receipt, storage, despatch, and transportation of closed pack excipients maintains material with the desired quality characteristics,
- assures product integrity, traceability, and consistent quality,
- avoids product contamination, and
- ensures that appropriate records are maintained.

Local regulations may have specific requirements, which shall be applied in addition to this standard.

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

An excipient can only be assigned as pharmaceutical grade when it complies with its Pharmacopeial specification (if existing for the specific excipient) and/or appropriate regulatory requirements and is manufactured, packaged, repackaged, and handled in accordance with excipient GMPs, GDPs and GWPs (e.g., IPEC Excipient GDP, WHO Excipient GTDP, NSF/IPEC/ANSI 363).

This document includes additional requirements that support the application of GWP to the receipt, storage, despatch, and transportation of packed 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.

0.2 Quality Management principles

No additional requirements to ISO 9001.

0.3 Process approach

0.3.1 General

No additional requirements to ISO 9001.

0.3.2 Plan-Do-Check-Act cycle

No additional requirements to ISO 9001.

0.3.3 Risk-based thinking

The storage and transportation of excipients is dependent on the nature of the infrastructure, climatic conditions, and the packaging used, so a "one size fits all" approach to the definition of excipient GWP is not possible. In such circumstances, utilising risk assessments at the excipient warehouse will identify those aspects of storage and transportation that require the implementation of GWP controls to minimise the threats to excipient quality, patient safety, and regulatory compliance. Storage and transportation may bring additional risks related to selection of materials, labelling and documentation errors that may be highly dependent on human error. Therefore, widespread use is made in this Annex to undertake and document risk assessments and their actions 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 warehouse operator may utilise those best suited to their circumstances.

Note: The methodologies detailed in ICH Q9 can be applied to this Annex.

0.4 Relationship with other Management System standards

No additional requirements to ISO 9001.

1 Scope

The scope of this Annex is the addition of GWP requirements for excipients to ISO 9001:2015. These principles are to be applied to the receipt, storage, issue, and transportation of excipients that remain in the original packaging as received into the warehouse. (See 4.3).

The Annex and its use

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

2 Normative References

ISO 9001:2015 Quality Management Systems – Requirements

3 Terms and Definitions

See Appendix 1 "Definitions and Glossary".

Pharmaceutical excipients

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 system.

4 Context of the Organisation

4.1 Understanding the organisation and its context

The organisation shall define and record their approach to GWP as internal issues. External and internal issues shall include outsourced services, (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

No additional requirements to ISO 9001.

Note: The regulatory authorities governing pharmaceutical products should be included as an interested party, even if they have no direct jurisdiction on the organisation.

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 with GWP for the warehousing and transportation of excipients.

The organisation shall establish and maintain supporting documentation or references that define the extent to which this Annex applies to its quality management system, its business processes, and the infrastructure.

4.4 Quality Management System and its processes

4.4.1

No additional requirements to ISO 9001.

4.4.2

No additional requirements to ISO 9001.

4.4.3

The quality management system documentation shall include:

a) the organisation's overall intentions and approach to GWP.
b) documented procedures required for conformance to this Annex.
c) documented risk assessment(s) that defines and justifies when the "if/as applicable" clauses in this Annex are not implemented.

Where warehouse storage, and other operations are outsourced the organisation shall:

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

NOTE 1: Outsourced operations will be audited as part of EXCiPACT GWP audits where they are included in the Scope of Certification (see ISO 17021 Annex Section 9.1.1).

NOTE 2: Quality risk management can be useful for identifying and 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 GWP 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 GWP for pharmaceutical excipients are determined, 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 GWP requirements.

5.2.2 Communicating the Quality Policy

No additional requirements to ISO 9001.

5.3 Organisational roles, responsibilities, and authorities

Note: Given the size and nature of warehousing and transportation operations, a full-time quality role may not be present on site as a matter of routine. Nevertheless, the following responsibilities need to be fulfilled.

Top management shall assign the authority and responsibility for:

f) a Quality responsible person or designee who shall be responsible at a minimum for:
- ensuring quality critical activities are identified and undertaken as defined,
- approving suppliers of quality critical materials and services,
- ensuring that significant deviations and complaints have been fully investigated, approved, and documented,
- ensuring corrective actions to address risks and opportunities are implemented,
- ensuring excipients are segregated if unsuitable for release,
- approving significant changes, (see 6.3),
- developing and implementing an internal audit program,
- ensuring that providers of outsourced services have agreed to comply with the relevant sections of this Annex,
- ensuring the promotion and awareness throughout the organisation of regulatory requirements concerning the storage and transportation of excipients.

6 Planning

6.1 Actions to address risks and opportunities

No additional requirements to ISO 9001.

6.2 Quality objectives and planning to achieve them

The quality objectives shall:

h) include objectives for 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 or any regulatory registrations. The organisation shall define the criteria for significant change. Evaluation and approval of changes shall occur prior to implementation. The Quality responsible person or designee shall approve significant changes that may impact on the quality of the excipient. Where the impact on the quality of the excipient is determined to be significant, such changes shall be communicated in advance whenever possible to customers and, as applicable, excipient manufacturers and/or regulatory authorities (see 8.2.1). Records of the change control process shall be retained.

Note: Excipient users need to know of significant changes so they can evaluate the impact on the quality of their products containing the excipient.

Changes notified by the excipient manufacturer that impact the quality of the excipient or any regulatory submissions made by the excipient manufacturer, shall be communicated to customers. (See also 8.2.1).

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

Note2: 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 are found to be implemented without prior approval, then they should be investigated as a nonconformity. (See 10.2).

7 Support

7.1 Resources

7.1.1 General

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

7.1.2 People

No additional requirements to ISO 9001.

7.1.3 Infrastructure

The infrastructure shall be designed, operated, cleaned, and maintained to avoid contamination and mix-ups of the excipient.

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

a) 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,
e) presence of airborne contaminants, especially dust, dirt, odours and highly sensitizing or toxic substances,

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

Defective equipment which can impact excipient quality shall be identified and repaired promptly.

Equipment, including racking, shall be constructed to facilitate cleaning and maintenance.

Highly sensitizing, odorous, or toxic materials shall be separated from excipients, unless measures to prevent contamination have been implemented.

Computerised systems that may impact excipient quality shall be demonstrated to be effective. There shall be controls to ensure consistent operation, the integrity of data, maintenance, back-up or archiving, disaster recovery and measures to prevent unauthorised access or changes to software, hardware, or data. Changes to computerised systems that may impact excipient quality shall be evaluated according to Section 6.3.

Note: Effectiveness may be demonstrated through historic performance data.

Access to buildings and facilities shall be controlled. Only designated personnel shall be allowed access to the storage, receipt, and despatch areas.

7.1.4 Environment for the operating of processes

The work environment shall be managed and controlled to assure excipient quality and prevent contamination. A documented risk assessment shall be carried out to determine the necessary controls. The risk assessment shall take into account any excipient supplier and / or customer requirements needed to ensure excipient quality.

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

a) controlled and monitored environments,
b) cleanliness conditions,
c) pest control,
d) personnel hygiene,
e) 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 Controlled and monitored environments

Where the excipient supplier, or the risk assessment has identified the need for a controlled environment (e.g., temperature, humidity, light), it shall be implemented and monitored to assure product quality and verified for effectiveness.

If interruptions to 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.

7.1.4.2 Cleaning conditions

The risk assessment shall define the extent and degree of cleanliness required. The organisation shall document procedures assigning responsibility for cleaning. 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.

7.1.4.3 Pest control

The risk assessment shall determine the type of pest control required. The organisation shall implement and document the pest control program.

7.1.4.4 Personnel hygiene

Personnel washing facilities shall be provided, which ensure defined hygiene standards can be maintained. Clean toilet facilities shall be separate from, but easily accessible to, working areas.

7.1.4.5 Lighting

Lighting shall facilitate cleaning, maintenance, and operations. If the lighting contains glass, brittle plastics etc. the risk assessment shall include an assessment for the potential impact of breakage.

7.1.4.6 Drainage

If the facility has internal drainage, the risk assessment shall include an assessment for the potential impact of contamination, including malodours, arising from drainage.

7.1.5 Monitoring and measuring of Resources

7.1.5.1 General

No additional requirements to ISO 9001.

7.1.5.2 Measurement traceability

No additional requirements to ISO 9001.

7.1.6 Organisational knowledge

The organisation shall have knowledge of the conditions and relevant regulations required to assure excipient quality during storage and transport.

7.2 Competence

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

Consultants advising on the storage and transport 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 assigned duties,
g) ensure training includes:
   i. GWP 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 product quality and use, due to departures from specified procedures,
   v. the reporting of significant failures and deviations from procedures,
h) ensure GWP 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 consequences of contamination.

7.4 Communication

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

Note: These requirements should be communicated in the language understood by the employees and contractors in the facility.

Top management shall be promptly notified about any quality critical situations (for example those that would lead to a product retrieval from the 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 quality management system documentation shall include:

c) the organisation's overall intentions and approach to GWP,
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 responsible person or designee shall review and approve documents that impact product quality, including changes to these documents.

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 handwritten 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.

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.

The record retention period shall be at least five years from the date of last receipt of the batch of the excipient.

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) implementing environmental and hygiene control programs to minimise risks of contamination of the excipient as identified in 7.1.3 and 7.1.4,
g) documenting procedures describing activities relating to the storage and distribution of excipients,
h) implementing identified actions from risk assessments described in other sections of this Annex.

8.2 Requirements for products and services

8.2.1 Customer communication

Communication with customers shall include:

f) notification of significant changes, including those notified by the excipient supplier (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 retrieval,
i) the transfer of information throughout the entire supply chain, including quality or regulatory information, from the original manufacturer of the excipient to the final customers,
j) for each batch, the original manufacturer's expiry and/or retest dates.

Certificates of Analysis shall be provided for each batch shipped.

If the original Manufacturer's COA is provided to customers, the details shall not be altered and the COA shall be traceable to the original Manufacturer's COA.

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

Changes requiring customer notification shall be determined.
The storage and transportation conditions shall comply with the excipient suppliers' recommendations.

8.2.3 Review of the requirements for products and services

No additional requirements to ISO 9001.

8.2.4 Changes to requirements for products and services

No additional requirements to ISO 9001.

8.3 Design and development of products and services

No additional requirements to ISO 9001.

8.3.1 General

No additional requirements to ISO 9001.

8.3.2 Design and development planning

No additional requirements to ISO 9001.

8.3.3 Design and development inputs

No additional requirements to ISO 9001.

8.3.4 Design and development controls

No additional requirements to ISO 9001.

8.3.5 Design and development outputs

No additional requirements to ISO 9001.

8.3.6 Design and development changes

No additional requirements to ISO 9001.

8.4 Control of externally provided processes, products, and services

8.4.1 General

Where operations that could affect excipient quality are outsourced, the organisation shall define:

a) the responsibility for quality and the control measures within the quality management system,
b) the applicable GWP principles in accordance with this Annex which are to be applied to those operations.

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

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

The organisation shall require that contractors adhere to the relevant sections of this Annex (See 4.4).

8.4.2 Type and extent of control

Where operations that could affect excipient quality are outsourced, the organisation shall demonstrate that the applicable GWP principles in accordance with this Annex are applied to those operations.

Incoming materials including labels shall be physically or administratively quarantined until they have been checked,

- that the identity and quantity match the delivery instructions,
- for the absence of damage,
- that the labels contain the correct information.

And additionally, for excipients,

- for the absence of, or damage to the excipient packaging seals,
- for the absence of contamination of the packaging.

The organisation shall define and document the controls used to verify the identity and quality of received excipient.

8.4.3 Information for external providers

Any GWP relevant activity outsourced to another party shall be agreed in a written contract including the application of the relevant parts of this annex.

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) For storage and handling operations written instructions shall be made available to the operator.

Records shall be retained for each batch of excipient stored and handled, Where critical to excipient quality, records shall include:

- date/time each step was completed or date/time log of key activities,
- identification of persons performing and directly supervising or checking each significant step, operation, or control parameter,
- conformance to any temperature and other controls required by the excipient manufacturer or defined by the organisation,
- any additional labelling,
- failures, deviations, and their investigations,
- inspection of the condition of the excipient external packaging on goods receipt and goods despatch.

Where additional labelling is used, the controls shall be documented and shall ensure:

- the original labels showing the excipient identity information remain unaltered and unobscured,
- correct labels are printed and issued containing the correct information,
- 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.

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

No additional requirements to ISO 9001.

c) The implementation of monitoring and measuring activities…,

No additional requirements to ISO 9001.

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

No additional requirements to ISO 9001.

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

No additional requirements to ISO 9001.

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,

No additional requirements to ISO 9001.

g) The implementation of actions to prevent human error,

No additional requirements to ISO 9001.

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

No additional requirements to ISO 9001.

8.5.2 Identification and traceability

The original manufacturer, intermediaries and handling operations of the excipient shall always be traceable, and the information made available on request (e.g., to the original manufacturer).

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

Documents that facilitate traceability and COAs shall be provided for each delivery as agreed with the customer.

8.5.3 Property belonging to customers or external providers

No additional requirements to ISO 9001.

8.5.4 Preservation

Storage conditions shall be maintained in accordance with the excipient manufacturers recommendations. They shall be monitored and recorded if they are critical for the maintenance of 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.

If applicable, suppliers of transport services shall be notified of, and agree to comply with any controlled conditions.

8.5.5 Post-delivery activities

No additional requirements to ISO 9001.

8.5.6 Control of changes

See Section 6.3.

8.6 Release of products and services

Excipient shall be released once it has been successfully checked for:

- agreement with the despatch documentation (e.g., identity, batch numbers, quantity),
- cleanliness,
- the absence of significant damage to the packaging and/or labels,
- the integrity of tamper evident seals.

Transportation, including containers shall be inspected to ensure it is clean and capable of providing the required protection to the excipient packs in transit.

Full container loads shall be secured using an approved container seal (e.g., ISO 17712).

Note: It is good practice to photograph the released excipient packs at the point of despatch.

8.7 Control of non-conforming outputs

8.7.1

The organisation shall deal with non-conforming outputs in one or more of the following ways:

e) segregation,
f) return of the material to the original supplier,
g) disposal.

There shall be procedures for the segregation and disposition of non-conforming excipient.

Incidences of non-conformance shall be investigated to assess the impact on other batches/excipients, and on processes and activities. (See 10.2).

Customer complaints and information about possible defects shall be systematically investigated and documented, based on a written procedure with assigned responsibilities.

There shall be a documented procedure defining how to manage excipient retrieval. All retrieval processes shall be documented, notified to the

original manufacturer and records retained. Retrieved materials shall be identified and quarantined.

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 responsible person or designee. 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 include the reason for return and the decision made as to the new disposition.

8.7.2

No additional requirements to ISO 9001.

9 Performance Evaluation

9.1 Monitoring, measurement, analysis, and evaluation

9.1.1 General

No additional requirements to ISO 9001.

9.1.2 Customer satisfaction

No additional requirements to ISO 9001.

9.1.3 Analysis and evaluation

No additional requirements to ISO 9001.

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 to ISO 9001.

9.3 Management review

9.3.1 General

No additional requirements to ISO 9001.

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).

9.3.3 Management review output

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

improvements necessary because of the review of regulatory requirements,

d) 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 to ISO 9001.

10.2 Nonconformity and corrective action

No additional requirements to ISO 9001.

10.3 Continual improvement

No additional requirements to ISO 9001.

CHANGES TO THE ISO 17021-1 ANNEX NECESSARY TO ACCOMMODATE THIS GWP ANNEX

Text in orange is additional to the existing text (black).

Audit Duration

9.1.3 Audit programme

9.1.3.1

Certification and recertification audits shall examine all GMP and / or GDP requirements. The Certification Body shall use the first audit in the two-stage audit Certification process to verify the scope of Certification and to determine the audit duration necessary for Certification, recertification, and surveillance audits. The two annual surveillance audits between Certifications shall cover at least the entire GMP and/or GDP requirements. The Certification Body shall re-evaluate the audit durations if there are significant changes to the auditees scope of Certification and/or activities.

Note: Assessment of a warehouse to the GWP Annex is only expected to take one day. (See 9.1.4.1).

If the warehouse is outsourced and it is included in the scope of the Certificate, then it shall be audited as part of the GWP assessment.

9.1.4 Determining audit time

Insert after the existing text and before the existing Note which is to be retained.

The audit time shall be determined according to the scope and activities of the GWP system to assess conformance to the excipient GWP requirements at each individual site.

As a minimum, audit durations for an EXCiPACT GWP stand-alone audit shall be:

- initial Certification: 1 day,
- surveillance Audit:1 day,
- recertification Audit:1 day.

In exceptional cases, less time than the minimum may be determined, however in such cases approval for such a deviation shall first be sought from EXCiPACT asbl.

Multi-site audits

Replace the existing 9.1. clause with the following:

9.1.5 Multi-site sampling

The Certification Body shall audit all sites at initial certification, surveillance, and recertification to the GMP / GDP requirements.

Multi-site sampling,

- EXCiPACT GMP/GDP.....Not permitted
- EXCIPACT GWP .....Permitted if the following conditions are met and maintained:
  - The Certification audit shall be completed without any major nonconformities which have not been addressed,
  - Thereafter, every site must be audited at least once every 3 years,
  - If one location has a major nonconformity then the location must be audited and may not be subject to further multi-site sampling until the observation has been addressed,
  - If any location has Life-Threatening or Critical nonconformities, or otherwise fails to meet the requirements, the whole certificate is suspended or withdrawn.

Note: Specific sites cannot be removed from scope because they perform badly.

Note: Auditor competency

No changes to this part of the Certification Standards**.**

Justification

GMP/GDP auditors will perform the GWP audit assessments. There is no relaxation of auditor competency requirements for assessment to the GWP annex. This follows the auditor competency requirements in the SQAS[7] scheme which are the same as EXCiPACT GMP/GDP, and keeps auditor competency simple, with just the one standard.

[7] See https://www.sqas.org/

EXCiPACT

Annex to ISO/IEC 17021-1:2015 Additional Requirements for Conformity Assessment Requirements for Certification Bodies and Auditors

Revision 2021

Foreword to ISO/IEC 17021-1:2015 Annex

Certification of a quality management system provides independent demonstration that the management system of the organisation:

a) conforms to specified requirements,
b) is capable of consistently achieving its stated policy and objectives,
c) is effectively implemented,
d) is regularly assessed.

This part of the set of EXCiPACT Standards provides specific requirements for Certification Bodies performing audit and certification in the field of an excipient GMP and GDP quality management system in addition to the requirements stipulated in ISO/IEC 17021-1:2015. Certification activities involve the audit of an organisation's quality management system. Observance of these requirements is intended to ensure that certification bodies operate quality management system certification in respect to a GMP and GDP quality management system in a competent, consistent, and impartial manner, thereby facilitating recognition of such bodies and acceptance of their certifications on a national and international basis.

ISO/IEC 17021-1:2015 "Conformity assessment - Requirements for bodies providing audit and certification of management systems - Part 1: Requirements" provides a set of requirements for management systems auditing at a generic level, aimed at providing a reliable determination of conformity to the applicable requirements for certification, conducted by a competent audit team, with adequate resources and following a consistent process, with the results reported in a consistent manner.

The requirements in ISO/IEC 17021-1:2015 are to be applied to the EXCiPACT Certification Scheme. This document sets out additional requirements to ISO/IEC 17021 for certification to EXCiPACT GMP and GDP quality management systems. Headings and sections in this document are those of ISO/IEC 17021-1:2015 and any additional text stipulates requirements to be implemented together with the ISO/IEC 17021-1:2015 clauses to perform EXCiPACT GMP and GDP certification assessments.

Where a heading or section of ISO/IEC 17021-1:2015 is omitted then there are no additional requirements to those already stipulated in ISO/IEC 17021-1:2015.

Thus, the requirements in this document will be simple to implement in organisations that are already using ISO/IEC 17021-1:2015 as the basis of their auditing, and for defining auditor competency.

The main text that follows is based on the headings in ISO/IEC 17021-1:2015 and the details are the EXCiPACT requirements:

Text in Bold are ISO/IEC 17021-1:2015 Headings

Standard Text are EXCiPACT requirements.

Italicised text is from ISO/IEC 17021-1:2015

Changes from the 1st Edition 2012

Due to the changes within ISO/IEC 17021-1:2015 in comparison to the 2006 edition it has been necessary to consolidate all the EXCiPACT requirements into this Annex rather than have an additional separate EXCiPACT Annex to ISO 19011:2011; the key requirements for auditing within that standard are now included in ISO/IEC 17021-1:2015.

In addition, changes have been included based on the feedback from Certification Bodies and suppliers of excipients who have been audited to EXCiPACT standards using the first edition.

Changes from the 2nd Edition 2017

Several clauses have been clarified and the actions to be taken when suspending or even withdrawing a certificate have been made clearer.

Remote audits have been allowed if conducted in accordance with the EXCiPACT instructions published on the website, which were necessary to accommodate the societal changes brought about by the COVID-19 pandemic.

1 Scope

The standard contains the principles and requirements for the quality management system operated by EXCiPACT registered Certification Bodies. The requirements ensure the impartiality, competence, and consistency of EXCiPACT audits and the certification of the quality management systems of excipient suppliers.

This second edition of this Annex includes requirements previously included in the ISO 19011:2002 annex for auditing to EXCiPACT standards. It therefore includes the principles of auditing, managing audit programmes, and the criteria for auditor competency. In the context of EXCiPACT audits, it indicates that auditors shall have the necessary knowledge and understanding of the principles and application of GMP and GDP. These requirements apply to auditors assessing an organisation's quality management system against the requirements in the EXCiPACT GMP and GDP Standards. In addition, those personnel making the certification decision in the Certification Bodies shall also comply with these requirements.

Where reference is made to EXCiPACT GMP or GDP standards, these may be substituted by other GMP or GDP standards which EXCiPACT asbl declares as equivalent.

2 Normative References

For dated references, the latest edition of the referenced document applies, if undated the current edition cited applies.

ISO/IEC 17021-1:2015 Conformity Assessment – Requirements for bodies providing audit and certification management systems – Part 1: Requirements.

ISO 9001 Quality Management Systems – Requirements.

Joint IPEC-PQG Good Manufacturing Practices Guide for Pharmaceutical Excipients 2006.

IPEC Good Distribution Practices Guide for Pharmaceutical Excipients 2006.

3 Terms and Definitions

Auditee	The organisation, including the sites named on the application, being assessed.
Certified Auditee:	Organisation whose quality management system has been certified.
Objective Evidence	Records, statements of fact or other information which can be verified and are relevant to the audit.
Certification Bodies	Independent third-party organisation that issues EXCiPACT Certificates based on the requirements in the EXCiPACT standards.
Technical Experts	Person who provides specific knowledge or expertise and independent advice to an audit team.
Technical Area	For the EXCiPACT Certification Scheme the ISO/IEC 17021 term "technical area" is defined by the context of the organisation (see ISO 9001:2015) and the boundaries within which EXCiPACT GMP and GDP are applied. Elsewhere EXCiPACT refers to the Technical Area as "Scope".

Nonconformities **Note:** ISO/IEC 17021-1:2015 defines Major and Minor nonconformities, but EXCiPACT has defined two further classifications related to the impact on product and patient safety (see also Section 9.4.5).	
Life Threatening	A nonconformity or other situation which has produced product that is harmful to the human or veterinary patient or a product which if released would be harmful to the human or veterinary patient.
Critical	The excipient poses significant risk to patient safety. Remediation before further excipient is produced would be indicated and/or a recall should be considered.
Major	No additional requirements.
Minor	No additional requirements.

4 Principles

4.1 General

No additional requirements.

4.2 Impartiality

Certification Bodies shall base decisions on objective evidence collected at audit, from which they can judge conformity or nonconformity to the current EXCiPACT GMP and/or GDP requirements. Such decisions shall not be influenced by other interests or other parties.

4.3 Competence

Note: Competency requirements for Certification Body personnel are set out in Section 7.1 and Annex A.

4.4 Responsibility

The auditee is responsible for conformance to ISO 9001 and EXCiPACT GMP or GDP certification requirements. The Certification Body is responsible for the assessment of the auditee against the certification requirements.

Note: EXCiPACT Certificates may be issued in combination with existing ISO 9001 Certificates or other standards recognised by EXCiPACT asbl.

4.5 Openness

No additional requirements.

4.6 Confidentiality

No additional requirements.

4.7 Responsiveness to complaints

No additional requirements.

4.8 Risk-based approach

No additional requirements.

5 General Requirements

5.1 Legal and contractual matters

5.1.1 Legal responsibility

No additional requirements.

5.1.2 Certification agreement

No additional requirements.

5.1.3 Responsibility for certification decisions

No additional requirements.

5.2 Management of impartiality

5.2.1

No additional requirements.

5.2.2

The Certification Bodies shall make publicly available (see 8.1.1.f) a statement that indicates it understands the criticality of impartiality in carrying out EXCiPACT certification assessments, that it manages conflicts of interest and ensures the objectivity of its certification activities.

5.2.3

No additional requirements.

5.2.4

No additional requirements.

5.2.5

No additional requirements.

5.2.6

No additional requirements.

5.2.7

No additional requirements.

5.2.8

No additional requirements.

5.2.9

No additional requirements.

5.2.10

To avoid a conflict of interest, personnel, including ex-employees or consultants, who have provided any management system consultancy (including GMP and/or GDP) shall not participate in audit or certification activities of the organisation within two years following the end of the consultancy.

5.2.11

No additional requirements.

5.2.12

No additional requirements.

5.2.13

No additional requirements.

5.3 Liability and financing

5.3.1

No additional requirements.

5.3.2

No additional requirements.

6 Structural Requirements

6.1 Organisational structure and top management

6.1.1

No additional requirements.

6.1.2

No additional requirements.

6.1.3

The Certification Body shall identify the top management (board, group or persons, or person) having overall authority and responsibility for the following:

k) Oversight of the appeals process.

6.1.4

No additional requirements.

6.2. Operational control

6.2.1

Risks to the competence, consistency and impartiality of the Certification Body arising from organisational arrangements for delivering certification activities shall be evaluated in accordance with 5.2.3.

6.2.2

The Certification Body shall justify the method and control of activities undertaken.

6.2.3

Top management shall record and inform EXCiPACT asbl of any instances where the impartiality of its activities has been compromised.

7 Resource Requirements

7.1 Competence of personnel

7.1.1 General considerations

Personnel involved in EXCiPACT certification activities shall meet the competency criteria in Annex A.

The Certification Body shall have processes to ensure that personnel have appropriate knowledge in GMP and / or GDP management in accordance with the requirements of Annex A.

The Certification Body shall ensure all EXCiPACT auditors are registered with EXCiPACT asbl.

7.1.2 Determination of competence criteria

No additional requirements.

7.1.3 Evaluation of processes

The Certification Body shall permit EXCiPACT asbl to witness an EXCiPACT certification audit each year.

Note: EXCiPACT asbl will share with the Certification Body their conclusions of the auditor evaluation following the witnessed audit.

A new auditor shall be witnessed performing an EXCiPACT audit by another EXCiPACT registered auditor or by a representative of EXCiPACT asbl before they perform audits independently.

Note: See also 7.2.11

At least every three years the Certification Body shall evaluate personnel involved in EXCiPACT certification activities to ensure that they retain the defined knowledge, skills and competencies as defined in 7.2. Records of the evaluation shall be retained.

The Certification Body shall require all EXCIPACT auditors to register with EXCIPACT asbl and to renew their registration every three years.

7.1.4 Other considerations

The Certification Body shall have access to the necessary technical expertise for advice on matters relating to excipient regulations, GMP and / or GDP within the geographic areas in which they operate.

7.2 Personnel involved in the certification activities

7.2.1

No additional requirements.

7.2.2

No additional requirements.

7.2.3

No additional requirements.

7.2.4

No additional requirements.

7.2.5

The Certification Body shall demonstrate that all auditors involved in performing EXCiPACT Certification audits meet the EXCiPACT auditor competency requirements and are registered with EXCiPACT asbl.

7.2.6

Auditors shall be knowledgeable of the EXCiPACT Certification Scheme requirements (see also Annex A).

7.2.7

The Certification Body shall identify on-going training needs and provide access to training for personnel involved in EXCiPACT Certification activities in accordance with 7.1.2.

7.2.8

Those individuals who are responsible for the decision to grant, maintain, renew, extend, reduce, suspend, or withdraw EXCiPACT GMP and/or GDP certification shall understand the EXCiPACT GMP and/or EXCiPACT GDP standards and certification requirements, shall be independent and free from conflict of interest of the audit process they are to review, and shall have proven knowledge and experience in the pharmaceutical and/or excipient industry.

Note: See also Annex A.

7.2.9

There shall be annual performance evaluation of those involved in the EXCiPACT certification programme plus assessment of audit skills every 3 years.

7.2.10

No additional requirements.

7.2.11

There shall be periodic on-site evaluation of auditor performance at least once in every 3-year period in accordance with EXCiPACT Auditor Competency Requirements. (See 7.1.3).

7.3 Use of individual external auditors and external technical experts

External auditors engaged by the Certification Body shall meet all requirements for EXCiPACT auditor competency (see Annex A) and shall be independent of the auditee and verified as free from conflicts of interest.

Note: External auditors may work for more than one Certification Body if these conditions are met on each occasion.

7.4 Personnel records

No additional requirements.

7.5 Outsourcing

7.5.1

The Certification Body shall have documented procedures for qualification and monitoring of outsourced services.

The Certification Body shall not outsource EXCiPACT certification to another organization.

Note: Use of external auditors is not outsourcing. (See 7.3.

7.5.2

No additional requirements.

7.5.3

No additional requirements.

7.5.4

No additional requirements.

8 Information Requirements

8.1 Public information

8.1.1

Information describing the EXCiPACT audit and certification process for granting, maintaining, extending, renewing, reducing, suspending, or withdrawing certification shall be publicly accessible.

Note: This EXCiPACT Standard and a list of EXCIPACT Certified organisations is publicly available at www.excipact.org.

8.1.2

If requested, the Certification Body shall provide information about:

d) the authenticity of an EXCiPACT Certificate and/or audit report(s)

8.1.3

No additional requirements.

8.2 Certification documents

The Certification Bodies shall permit the auditee to disclose audit reports and any associated documentation (e.g., Corrective Action Plan).

8.2.1

No additional requirements.

8.2.2

No additional requirements.

Note concerning bullet f):

- EXCiPACT GMP applies excipient manufacturers,
- EXCiPACT GDP applies to excipient distributors,
- EXCiPACT GMP and GDP applies to organisations performing both excipient manufacture and excipient distribution activities.

8.3 Reference to certification and use of marks

8.3.1

The Certification Bodies shall comply with the requirements in the legal agreement with EXCiPACT asbl and with the guidance provided by EXCiPACT for the use of EXCiPACT logo and name.

8.3.2

No additional requirements.

8.3.3

No additional requirements.

8.3.4

No additional requirements.

8.3.5

The Certification Bodies shall exercise proper control of ownership and take action to deal with incorrect references to certification status or misleading use of certification documents, marks, or audit reports.

The Certification Bodies shall notify EXCiPACT of any such incidents relating to EXCiPACT certification activities.

8.4 Confidentiality

Proprietary information in the EXCiPACT report may be redacted or made unreadable, if the Certification Bodies agrees the redactions are not material to the Certification status. (See also 9.4.8.3).

8.4.1

No additional requirements.

8.4.2

No additional requirements.

8.4.3

The Certification Bodies shall have a written agreement with the certified client that it will respond to requests for authenticating Certificates and Audit reports from third parties without the need for the certified client's consent.

8.4.4

No additional requirements.

8.4.5

No additional requirements.

8.4.6

No additional requirements.

8.4.7

No additional requirements.

8.5 Information exchange between a Certification Body and its clients

8.5.1 Information on the certification activity and requirements

The Certification Body shall provide information and update clients on the following:

g) The requirement to pay EXCiPACT a Certificate Fee before an EXCiPACT Certificate (or renewed certificate) can be issued.

8.5.2 Notice of changes by a Certification Body

Upon receipt of changes from EXCiPACT asbl, an implementation plan shall be developed by the Certification Bodies comprising the following:

- description of the change to the Certification Programme,
- potential impact of the change to auditees and auditees already certified,
- establishment of a future effective date by which all auditees shall comply with the new requirements,
- methods of verifying that the auditees have implemented the changes.

Following implementation, there shall be a review of confirmatory documentation, or on-site verification at the next scheduled site audit that changes have been implemented.

8.5.3 Notice of changes by a certified client

No additional requirements.

9 Process Requirements

9.1 Pre-certification activities

9.1.1 Application

Where the auditee has an ISO 9001 quality management system then the EXCiPACT GMP and/or GDP Certification Scope shall not encompass more than the Certification Scope of the ISO 9001 quality management system.

9.1.2 Application review

9.1.2.1

The Certification Bodies shall conduct a review of the application and supplementary information for certification to ensure that:

e) the certification is for Excipient GMP and/or Excipient GDP,

f) any health and safety requirements for the auditors have been identified.

9.1.2.2

No additional requirements.

9.1.2.3

No additional requirements.

9.1.3 Audit programme

9.1.3.1

Certification and recertification audits shall examine all GMP and / or GDP requirements. The Certification Body shall use the first audit in the two-stage audit Certification process to verify the scope of Certification and to determine the audit duration necessary for Certification, recertification, and surveillance audits. The two annual surveillance audits between Certifications shall cover at least the entire GMP and/or GDP requirements. The Certification Body shall re-evaluate the audit durations if there are significant changes to the auditees scope of Certification and/or activities.

Note: Assessment of a warehouse to the GWP Annex is only expected to take one day. (See 9.1.4.1).

If the warehouse is outsourced and it is included in the scope of the Certificate, then it shall be audited as part of the GWP assessment.

9.1.3.2

No additional requirements.

9.1.3.3

No additional requirements.

Note: See also the Guidance on the Frequency of EXCiPACT Surveillance and Recertification Audits on the EXCiPACT website.

9.1.3.4

No additional requirements.

9.1.3.5

No additional requirements.

9.1.4 Determining audit time

9.1.4.1

The audit time shall be determined according to the scope and complexity of the GMP / GDP system and excipients produced in order to assess conformance to the excipient GMP / GDP requirements at each individual site.

As a minimum, audit durations for an EXCiPACT GMP/GDP stand-alone audit shall be:

- initial Certification: 2 days,
- surveillance Audit:1 day,
- recertification Audit:2 days.

The audit time shall be determined according to the scope and activities of the GWP system to assess conformance to the excipient GWP requirements at each individual site.

As a minimum, audit durations for an EXCiPACT GWP stand-alone audit shall be:

- initial Certification: 1 day,
- surveillance Audit:1 day,
- recertification Audit:1 day.

In exceptional cases, less time than the minimum may be determined, however in such cases approval for such a deviation shall first be sought from EXCiPACT asbl.

In exceptional cases, less time than the minimum may be determined as appropriate, however in such cases approval for such a deviation shall first be sought from EXCiPACT asbl.

Note: See Annex F for guidance on audit durations.

9.1.4.2

In determining the audit time, the Certification Body shall consider, among other things, the following aspects:

i) the number of excipients in scope,
j) the complexities of the activities at each location,
k) any other activities within the scope of the certification.

Note: The audit time determined should be verified as suitable at the Stage 1 audit. (See 9.3.1.2).

Note: See Annex F for guidance on audit durations.

9.1.4.3

The justification for GMP/GDP audit times shall be documented and records retained of each decision for each auditee.

9.1.4.4

No additional requirements.

9.1.5 Multi-site sampling

The Certification Bodies shall audit all sites at initial certification, surveillance, and recertification to the GMP / GDP requirements.

Multi-site sampling.

- EXCiPACT GMP/GDP: Not permitted
- EXCIPACT GWP: Permitted if the following conditions are met and maintained:
  - The Certification audit shall be completed without any major nonconformities which have not been addressed,
  - Thereafter, every site must be audited at least once every 3 years,
  - If one location has a major nonconformity then the location must be audited and may not be subject to further multi-site sampling until the observation has been addressed,
  - If any location has Life-Threatening or Critical nonconformities, or otherwise fails to meet the requirements, the whole certificate is suspended or withdrawn.

Note: Specific sites cannot be removed from scope because they perform badly.

9.1.6 Multiple management systems standards

No additional requirements.

9.2 Planning audits

9.2.1 Determining audit objectives, scope, and criteria

9.2.1.1

The Certification Bodies shall request the following documentation for review prior to the site audit:

- documentation describing conformance to the GMP / GDP standards and the required scope of the audit,
- documentation showing the layout and size of the excipient operations conducted at the facility,
- current organisation chart.

9.2.1.2

The Certification Bodies shall not communicate areas for potential improvement against the EXCiPACT GMP or GDP Standards.

9.2.1.3

The audit shall cover the following:

- GMP covering all operations performed to produce the excipient from the point at which full GMP begins through to storage and shipment of the packaged excipient where the applicant is a manufacturer and / or,
- GDP where the applicant is a distributor or a manufacturer distributing excipients, and / or
- GWP where the applicant stores and may be responsible for the transport, of excipients in the original packaging

Note: A combined certificate showing one or more of these GxPs may be issued in accordance with the scope of certification.

Where audits are being planned for multiple sites, the requirements of Section 9.1.5 shall be addressed.

9.2.1.4

No additional requirements.

9.2.2 Audit team selection and assignments

9.2.2.1 General

The auditee and the auditors shall be notified of the intended auditors prior to the assessment,

- both the auditors and the auditee have a duty to notify the Certification Bodies if there is any conflict of interest with the assignment,
- if there is any conflict of interest, then other auditors shall be assigned. (See also 9.2.3.5).

9.2.2.1.1

Where the audit is conducted to certify conformance with ISO 9001 plus the GMP/GDP Standard, the audit team shall include an ISO 9001 Registered Lead Auditor and at least one team member shall be an EXCiPACT Auditor meeting the competency criteria in Section 7. Where the audit is conducted solely to the GMP/GDP Standard (or another EXCiPACT declared equivalent standard), the audit team does not require an ISO 9001 Registered Lead Auditor.

9.2.2.1.2

No additional requirements.

Note: Ideally, the same auditor should not audit the same client more than three times consecutively, however auditor availability in the location may not permit a rotation between approved EXCiPACT auditors.

9.2.2.1.3

No additional requirements.

9.2.2.1.4

No additional requirements.

9.2.2.1.5

No additional requirements.

9.2.2.2 Observers, technical experts, and guides

9.2.2.2.1

No additional requirements.

9.2.2.2.2

No additional requirements.

9.2.2.2.3

No additional requirements.

9.2.3 Audit plan

9.2.3.1

No additional requirements.

9.2.3.2

The audit plan shall at least include or refer to the following:

e) *the expected duration of on-site activities;* a minimum of 30% of the total time shall be in operational areas.

An audit may be performed remotely if in compliance with the EXCiPACT Annex on conducting remote audits.

Note: For the duration of the COVID-19 pandemic, as in accordance with national legislation and the availability of international travel, the prohibition on remote audits is suspended. See EXCiPACT website for the Annex which describes when and how remote audits may be used.

Note: See 9.1.4 for guidance on EXCiPACT audit durations.

9.2.3.3

No additional requirements.

9.2.3.4

No additional requirements.

9.2.3.5

No additional requirements.

9.3 Initial certification

9.3.1 Initial certification audit

9.3.1.1. General

No additional requirements.

9.3.1.2 Stage 1

9.3.1.2.1

A formal audit plan shall be prepared for Stage 1 audits.
The Stage 1 audit shall be conducted on site. The Stage 1 audit shall be used to justify the Stage 2 audit plan.

9.3.1.2.2

No additional requirements.

9.3.1.2.3

No additional requirements.

9.3.1.2.4

The interval between a Stage 1 and Stage 2 audit shall not exceed 6 months.

9.3.1.3 Stage 2

The purpose of the Stage 2 audit is to evaluate the implementation, including effectiveness, of the client's management system. The Stage 2 audit shall take place at the site(s) of the client. It shall include at least the following:

g) information and evidence of conformity to the GMP / GDP standards.

9.3.1.4 Initial certification conclusions

No additional requirements.

9.4 Conducting audits

9.4.1 General

The Certification Bodies shall have a documented process for conducting on site GMP / GDP audits.

Virtual audits shall not be conducted for EXCiPACT GMP or GDP purposes.

9.4.2 Conducting the opening meeting

No additional requirements.

9.4.3 Communication during the audit

No additional requirements.

9.4.4 Obtaining and verifying information

No additional requirements.

9.4.5 Identifying and recording audit findings

9.4.5.1

No additional requirements.

9.4.5.2

The Certification Bodies shall not communicate areas for potential improvement against the EXCiPACT GMP or GDP Standards.

Note: Opportunities for potential improvement could be perceived as consultancy.

9.4.5.3

Nonconformities shall be classified as:

- life threatening, or
- critical, or
- major, or
- minor.

9.4.5.4

No additional requirements.

9.4.6 Preparing audit conclusions

No additional requirements.

9.4.7 Conducting the closing meeting

No additional requirements.

9.4.8 Audit report

9.4.8.1

EXCiPACT audit reports shall be prepared in English. The client shall be permitted to share copies of the complete audit report with their customers. Where requested by the client's customers, the Certification Body shall verify that copies of the audit report are complete and a true record.

Note: A translated copy of the audit report may be prepared in another language if requested by the client.

9.4.8.2

The audit report shall disclose any areas of excipient GMP and/or GDP requirements that were not covered.

Any nonconformities remedied during the audit shall be classified as in 9.4.5.3 and noted accordingly in the audit report.

Any nonconformities remedied after the audit and prior to the certification decision shall be classified as in 9.4.5.3 and noted accordingly in a suitably revised audit report.

9.4.8.3

The audit report shall include:

- the operational activities examined,
- the excipients and grades covered,
- a list of the client's personnel involved in the audit.

Proprietary information in the EXCiPACT report may be redacted or made unreadable by the certified organisation, if the Certification Bodies agrees the redactions are not material to the Certification status. (See also 8.4).

The audit report shall not include opportunities for improvement against the GMP / GDP Standards.

Note: The EXCiPACT website contains more guidance on the audit report contents.

9.4.9 Cause analysis of nonconformities

The auditee shall be required to submit a corrective action plan for all nonconformities, and this shall be included with the audit report for review under 9.5.

9.4.10 Effectiveness of corrections and corrective actions

The auditee shall be required to provide evidence of the progress of any corrective action plans in accordance with the timings defined in the plans.

The Certification Bodies shall ensure an EXCiPACT Registered auditor verifies the adequacy of corrective action plans.

The progress of the corrective action plan shall be verified on site at the next audit(s).

Additional Audits

A further on-site audit is required to verify the effectiveness of any correction and corrective actions for Life Threatening and Critical nonconformities. Major nonconformities can be verified remotely where the client provides objective evidence that they have addressed the issue and by direct observation at the next audit.

9.5 Certification decision

No additional requirements.

9.5.1 General

9.5.1.1

Individuals responsible for the decision to grant, maintain, renew, extend, reduce, suspend, or withdraw an EXCiPACT GMP and/or GDP certificate shall understand the EXCiPACT GMP and/or EXCiPACT GDP standards and certification requirements. These individuals shall be independent and free from conflict of interest of the audit process they are to review and shall have proven knowledge and experience in the pharmaceutical and/or excipient industry.

Note: See Annex A.

9.5.1.2

No additional requirements.

9.5.1.3

No additional requirements.

9.1.5.4

No additional requirements.

9.5.2 Actions prior to making a decision

The Certification Body shall have a process to conduct an effective review prior to making a decision for granting certification, expanding, or reducing the scope of certification, renewing, suspending, or restoring, or withdrawing of certification, including, that

d) the audit report complies with the requirements of 9.4.8,
e) correction and corrective action plans for all Life Threatening, Critical and Major nonconformities have been reviewed, accepted, and verified.

9.5.3 Information for granting initial certification

For Certification, the acceptance criteria are:

1. No items rated as Life Threatening,
2. No items rated as Critical,
3. No items rated as Major.

For continuing Certification, the Surveillance audit shall have:

1. No items rated as Life Threatening or Critical,
2. No items rated as Major unless the deficiency has been remediated or an interim control is in-place i.e., Corrective Action plan accepted by the Certification Bodies and verified,

3. No items rated as Minor from a prior audit that have either not been corrected or for which an acceptable Corrective Action plan has not been developed.

The certification decision shall be made by at least two persons, one of whom should meet the competency requirements for an EXCiPACT GMP/ GDP auditor (see Annex A).

9.5.3.1

No additional requirements.

9.5.3.2

If the Certification Body is not able to verify the implementation of corrections and corrective actions of any Life Threatening or Critical nonconformity within 6 months after the last day of the stage 2, the Certification Body shall conduct another stage 2 prior to recommending certification.

9.5.3.3

When transferring certification, the recertification date on the last certificate cannot be extended without another full certification audit.

9.5.4 Information for granting recertification

No additional requirements.

9.6 Maintaining certification

No additional requirements.

9.6.1 General

The Certification Body shall maintain certification based on demonstration that the client continues to satisfy the requirements of the management system standard. It may maintain a client's certification based on a positive conclusion by the audit team leader without further independent review and decision, provided that:

c) for any Life Threatening or Critical nonconformity that may lead to suspension or withdrawal of certification, the Certification Body has a system that requires the audit team leader to report to the Certification Body the need to initiate a review by competent personnel (see 7.2.8), different from those who carried out the audit, to determine whether certification can be maintained.

9.6.2 Surveillance activities

9.6.2.1 General

No additional requirements.

9.6.2.2 Surveillance audit

Surveillance audits shall be conducted at least annually and cover at least half of the quality system such that the entire excipient quality system will be reviewed by the two surveillance audits that occur in between recertification audits.

9.6.3 Recertification

9.6.3.1 Recertification audit planning

9.6.3.1.1

Recertification shall occur at intervals of not more than three years after initial certification or last recertification. The recertification audit shall be planned and conducted to confirm that the requirements of excipient GMP /GDP continue to be met.

Note: See also the Guidance on the Frequency of EXCiPACT Surveillance and Recertification Audits on the EXCiPACT website.

9.6.3.1.2

No additional requirements.

9.6.3.1.3

No additional requirements.

9.6.3.2 Recertification audit

9.6.3.2.1

No additional requirements.

9.6.3.2.2

For any Life Threatening, Critical or Major nonconformity, the Certification Body shall define time limits for correction and corrective actions. These actions shall be implemented and verified prior to issue of the new certificate.

9.6.3.2.3

A new certificate shall not be issued with a period of validity more than 39 months from the date or the recertification audit.

9.6.3.2.4

If the Certification Body has not completed the recertification audit or the Certification Body is unable to verify the implementation of corrections and corrective actions for any Life Threatening or Critical nonconformity (see 9.5.2.1) prior to the expiry date of the certification, then recertification shall not be recommended, and the validity of the certification shall not be

extended. The client shall be informed, and the consequences shall be explained.

9.6.3.2.5

No additional requirements.

9.6.4 Special audits

9.6.4.1 Expanding scope

No additional requirements.

9.6.4.2 Short notice audits

No additional requirements.

9.6.5 Suspending, withdrawing, or reducing the scope of certification

9.6.5.1

Certifications granted, suspended, or withdrawn must be reported without delay to EXCiPACT, who will make such information publicly available.

9.6.5.2

The Certification Body shall suspend certification in cases when, for example:

- A regulatory authority has identified a Life Threatening or Critical Nonconformity from GMP/GDP requirements,
- The certified client has persistently failed to:
  - Comply with the requirements of a relevant competent authority,
  - Breached the laws or legally binding regulations regarding the products or processes covered by the EXCiPACT Certification,
  - Failed to comply with the EXCiPACT certification scheme regulations or those of the Certification Body, including misuse of the Certificate, audit report(s) or EXCiPACT logo,
  - Failed to pay invoices for activities carried out by the Certification Body or to EXCiPACT,
  - Engaged in intentional deception.

Other persistent and serious failures may also trigger suspension of Certification.

The Certification notify shall immediately notify EXCiPACT if a Certificate is Suspended.

9.6.5.3

The Certification Body shall have enforceable arrangements with its clients to ensure that in case of suspension, the client refrains from further promotion of its certification. The Certification Body shall inform EXCIPACT of the suspended status of the certification. (See 9.6.5.1).

9.6.5.4

The Certification body shall immediately notify EXCiPACT if a Certificate is withdrawn.

9.6.5.5

No additional requirements.

9.7 Appeals

9.7.1

No additional requirements.

9.7.2

No additional requirements.

9.7.3

No additional requirements.

9.7.4

The appeals handling process shall include at least the following elements and methods:

d) where the appeal concerns EXCiPACT Certification and it cannot be resolved to the satisfaction of the auditee using the standard Certification Bodies appeals procedure, the appellant shall be informed they have the right to request EXCiPACT asbl to review the decision.

9.7.5

No additional requirements.

9.7.6

When a final decision is communicated and the decision is not accepted, the appellant shall be notified that they may request EXCiPACT to review the decision.

9.7.7

No additional requirements.

9.7.8

No additional requirements.

9.8 Complaints

9.8.1

No additional requirements.

9.8.2

No additional requirements.

9.8.3

No additional requirements.

9.8.4

No additional requirements.

9.8.5

No additional requirements.

9.8.6

The complaints-handling process shall include at least the following elements and methods:

d) EXCiPACT shall be notified of all complaints about the EXCiPACT Certification Scheme and their outcomes,

e) where the complaint concerns EXCiPACT Certification and it cannot be resolved to the satisfaction of the complainant using the standard Certification Bodies complaints procedure, the complainant shall be informed that they have the right to request EXCiPACT asbl to review the decision.

9.8.7

No additional requirements.

9.8.8

No additional requirements.

9.8.9

No additional requirements.

9.8.10

No additional requirements.

9.8.11

No additional requirements.

9.9 Client records

9.9.1

No additional requirements.

9.9.2

No additional requirements.

9.9.3

No additional requirements.

9.9.4

Records of EXCiPACT Certification shall be retained for a minimum of 6 years.

Note: The Certification Body is required to verify the authenticity of audit reports and this service may need to be provided for any reports issued in the previous 6 years.

10 Management System Requirements for Certification Bodies

10.1 Options

No additional requirements.

10.2 Option A: General management system requirements

10.2.1 General

The Certification Body shall appoint a member of management who, irrespective of other duties, shall have the responsibility and authority that includes:

a) ensuring the processes and procedures needed for the management system are established, implemented, and maintained,

b) reporting to top management on the performance of the management system and any need for improvement.

10.2.2 Management system manual

No additional requirements.

10.2.3 Control of documents

No additional requirements.

10.2.4 Control of records

No additional requirements.

10.2.5 Management review

10.2.5.1

No additional requirements.

10.2.5.2

No additional requirements.

10.2.5.3

No additional requirements.

10.2.6 Internal audits

10.2.6.1

No additional requirements.

10.2.6.2

No additional requirements.

10.2.6.3

No additional requirements.

10.2.6.4

No additional requirements.

10.2.7 Corrective actions

No additional requirements.

10.3 Option B: Management system requirements in accordance with ISO 9001

10.3.1 General

No additional requirements.

10.3.2 Scope

No additional requirements.

10.3.3 Customer focus

No additional requirements.

10.3.4 Management review

No additional requirements.

Annex A (normative) Required Knowledge and Skills

A.1 General

Table A.1 – Table of knowledge and skills

Additional EXCiPACT requirements (all other entries as ISO/IEC 17021-1:2015)

Knowledge and skills	Conducting the application review to determine audit team competence required, to select the audit team members, and to determine the audit time	Reviewing audit reports and making certification decisions	Auditing and leading the audit team
Qualifications requirements for EXCiPACT			See A.1.1
Knowledge of business management practices	See A.2.1	See A.2.1	

A.1.1 Qualification requirements for EXCiPACT auditors

EXCiPACT Auditors shall meet the knowledge and competency criteria in this Annex.

EXCiPACT Auditors shall also hold at least one of the following:

- registtation as a quality management systems Auditor by an accredited Certification Bodies,
- registeration with a recognised auditor registration organisation, (e.g., International Register of Certificated Auditors (IRCA), American Society for Quality (ASQ)),

have demonstrated their ability to perform management system audits such as ISO 9001, ISO 14001, audits or pharmaceutical or excipient or API GMP/GDP audits and completed at least 5 audits in the last two years.

EXCiPACT Auditors shall have:

a) A tertiary scientific qualification,

Note: Examples of such qualifications are Higher National Diploma (UK), Associates Degree (US.).

b) A minimum of five years quality related work experience, such as:
   - a Technical, Managerial, or Professional role within:
     - ✓ an excipient or API supplier,
     - ✓ a pharmaceutical company.
   - a role with responsibilities that include conformance to GMP requirements,
   - performing quality system or GMP audits of chemical operations to a recognised standard, e.g., ISO 9001.

c) A registration with the EXCiPACT auditor registration scheme (see www.excipact.org) which includes:
   i. attendance at an EXCiPACT approved auditor training course which includes a minimum of 7 contact hours applicable to GMP and GDP for excipients,
   ii. a satisfactory examination result after attending an EXCiPACT approved auditor training course,
   iii. successful completion of one audit witnessed by an EXCiPACT approved observer, demonstrating acceptable:
     - ✓ audit skills,
     - ✓ knowledge of excipient GMP conformance requirements,
     - ✓ preparation of audit reports,
     - ✓ appropriate rating of findings.

Note: A successful witnessed audit is where the auditor has demonstrated their skills in planning, conducting, and documenting an audit.

A.2 Competency requirements for management system auditors

A.2.1 Knowledge of business management practices

No additional requirements.

A.2.2 Knowledge of audit principles, practices, and techniques

Auditors shall demonstrate the ability to apply a breadth of knowledge and skills which will enable them to be effective in respect of ensuring that GMP and GDP audits are conducted in a consistent manner.

- reaching agreement with the excipient supplier to audit findings and conclusions,
- effectively reviewing the resulting correction and corrective actions arising from EXCiPACT Certification audits.

A.2.3 Knowledge of specific management system standards/ normative references

Auditors shall have current knowledge of:

- management system definitions,
- industry guidance,
- relevant legislation,
- the application of excipient GMPs to different excipient production processes,
- regulatory requirements for the excipient in the intended markets, for example:
  a. basic microbiology and chemistry,
  b. appropriate Pharmacopoeias,
  c. cleaning principles as applied to manufacturing processes,
  d. IPEC-PQG Excipient GMPs,
  e. regulations in the intended market (e.g., TSE, Residual Solvents),
  f. risk assessment techniques (ICH Q9, HACCP, etc.).
- information systems and technology used in GMP and GDP operations (demonstration of the proper use and control of computer systems),
- good distribution practices, including:
  a. the different operations of distributors,
  b. operations involving repackaging and relabelling of excipients,
  c. office-only operations,
  d. an understanding of distribution related safety and quality systems:
     1. responsible Care and/or Responsible Distribution Programmes,
     2. distributors assessment systems (e.g., for Europe Safety Quality Assessment Systems; European Single Assessment for Chemical Distributors (SQAS ESAD II)).

A.2.4 Knowledge of Certification Body's processes

Auditors shall have knowledge of the processes required for EXCiPACT auditing and certification.

A.2.5 Knowledge of client's business sector

Auditors shall have knowledge and understanding of:

- business processes affecting the excipient and pharmaceutical industries,
- terminology used by the excipient and pharmaceutical industries,
- methods used to distribute excipients.

A.2.6 Knowledge of client's products, processes, and organisation

Auditors shall have knowledge and understanding of:

- the science and technology of excipient manufacture and distributor operations,
- the critical activities that assure excipient quality,
- the relevance of the functionality of the excipient to the finished dosage form,
- the relevance of the route of administration of the finished dosage form in terms of the GMP and GDP to be applied to the excipient,
- the differing operations to produce the excipient ranging from mineral extraction and purification to chemical or biochemical synthesis.

A.2.7 Language skills appropriate to all levels within the client organisation

No additional requirements.

A.2.8 Note-taking and report-writing skills

No additional requirements.

A.2.9 Presentation Skills

No additional requirements.

A.2.10 Interviewing skills

No additional requirements.

A.2.11 Audit-management skills

No additional requirements.

A.3 Competence requirements for personnel reviewing audit reports and making certification decisions

A.3.1 Knowledge of audit principles, practices, and techniques

Personnel reviewing audit reports shall demonstrate the ability to apply a breadth of knowledge and skills which will enable them to be effective in respect of ensuring that GMP and GDP audits are conducted in a consistent manner.

- reaching agreement with the excipient supplier to audit findings and conclusions,
- effectively reviewing the resulting correction and corrective actions arising from EXCiPACT Certification audits.

A.3.2 Knowledge of specific management system standards/ normative references

Personnel reviewing audit reports shall have current knowledge of:

- management system definitions,
- industry guidance,
- relevant legislation,
- the application of excipient GMPs to different excipient production processes.
- regulatory requirements for the excipient in the intended markets, for example:
  a. basic microbiology and chemistry,
  b. appropriate Pharmacopoeias,
  c. cleaning principles as applied to manufacturing processes,
  d. IPEC-PQG Excipient GMPs,
  e. regulations in the intended market (e.g., TSE, Residual Solvents),
  f. risk assessment techniques (ICH Q9, HACCP, etc.).
- information systems and technology used in GMP and GDP operations (demonstration of the proper use and control of computer systems),
- good distribution practices, including:
  a. the different operations of distributors,
  b. operations involving repackaging and relabelling of excipients
  c. office-only operations,
  d. an understanding of distribution related safety and quality systems:
     1. responsible care and/or responsible distribution programmes,
     2. distributors assessment systems (e.g., for Europe Safety Quality Assessment Systems; European Single Assessment for Chemical Distributors (SQAS ESAD II)).

A.3.3 Knowledge of Certification Body's processes

Personnel reviewing audit reports shall have knowledge of the processes required for EXCiPACT auditing and certification.

A.3.4 Knowledge of client's business sector

Personnel reviewing audit reports shall have knowledge and understanding of:

- business processes affecting the excipient and pharmaceutical industries,
- terminology used by the excipient and pharmaceutical industries,
- methods used to distribute excipients.

A.4 Competence requirements for personnel conducting the application review to determine the audit team competence required, to select the audit team members, and to determine the audit time

A.4.1 Knowledge of specific management system standards /normative references

Personnel conducting the application review etc. shall have current knowledge of:

- management system definitions,
- industry guidance,
- relevant legislation,
- the application of excipient GMPs to different excipient production processes,
- regulatory requirements for the excipient in the intended markets, for example:
  a. basic microbiology and chemistry,
  b. appropriate Pharmacopoeias,
  c. cleaning principles as applied to manufacturing processes,
  d. IPEC-PQG Excipient GMPs,
  e. regulations in the intended market (e.g., TSE, Residual Solvents),
  f. risk assessment techniques (ICH Q9, HACCP, etc.).
- information systems and technology used in GMP and GDP operations (demonstration of the proper use and control of computer systems),
- good distribution practices, including:
  a. the different operations of distributors,
  b. operations involving repackaging and relabelling of excipients,
  c. office-only operations,
  d. an understanding of distribution related safety and quality systems:
     1. responsible Care and/or Responsible Distribution Programmes,
     2. distributors assessment systems (e.g., for Europe Safety Quality Assessment Systems; European Single Assessment for Chemical Distributors (SQAS ESAD II)).

A.4.2 Knowledge of Certification Body's processes

Personnel conducting the application review etc. shall have knowledge of the processes required for EXCiPACT auditing and certification.

A.4.3 Knowledge of client's business sector

Personnel conducting the application review etc. shall have knowledge and understanding of:

- business processes affecting the excipient and pharmaceutical industries,
- terminology used by the excipient and pharmaceutical industries,
- methods used to distribute excipients.

A.4.4 Knowledge of client's products, processes, and organisation

Personnel conducting the application review etc. shall have knowledge and understanding of:

- the science and technology of excipient manufacture and distributor operations,
- the critical activities that assure excipient quality,
- the relevance of the functionality of the excipient to the finished dosage form,
- the relevance of the route of administration of the finished dosage form in terms of the GMP and GDP to be applied to the excipient,
- the differing operations to produce the excipient ranging from mineral extraction and purification to chemical or biochemical synthesis.

Annex B (informative) Possible Evaluation Methods

B1 General

No additional Guidance

B2 Review of records

- an annual review of audit reports issued by the auditor,
- analysis of new records of further education, training, employment, and excipient GMP / GDP audit experience since the last review.

B3 Feedback

- surveys, questionnaires, complaints, etc. from applicants and others,
- audit Team Leader (if there was one) feedback on team participants (and vice versa).

B4 Interviews

No additional Guidance

B5 Observations

- any observation of audit skills, (e.g., report from an EXCiPACT asbl witness or a certification Body witness).

B6 Examinations

No additional Guidance

Annex C (informative) Examples of a Process Flow for Determining and Maintaining Competence

No additional requirements.

Annex D (informative) Desired Personal Behaviour

Examples of personal behaviours that are important for personnel involved in certification activities for any type of management system are described as follows:

n) sound judgement,
o) integrity,
p) proven ability to put people at ease and understand the auditee's perspective,
q) proven ability to assure conduct of the audit to the audit schedule and within the scope.

Ethical Conduct includes:

- not accepting any inducements that may affect decision-making,
- not disclosing any confidential information to a third party without written authorisation,
- not practicing when barred.

Fair Presentation includes:

- truthful audit reports,
- accurate report content,
- report of obstacles and unresolved opinions.

Due Professional Care:

- the auditor should only undertake assignments for which they are qualified, e.g., Audit a quality management system for conformance to levels of GMP or GDP for which the auditor has been trained and qualified in accordance with EXCiPACT Auditor Competency and Qualification Requirements.

Independence includes:

- demonstrate lack of bias and conflict of interest,
- financial independence,
- organisational independence,
- evidence-based rather than subjective.

Annex E (informative) Audit and Certification Process

No additional guidance

Annex F (informative) Determination of Audit Duration

This annex provides guidance on Clause 9.1.4 Determining Audit Time.

The mandated durations are given based on an independent EXCiPACT audit. Where a combined ISO 9001 and EXCiPACT audit is conducted additional time should be added to allow for assessment of the ISO 9001 requirements.

Where an audit is conducted against the requirements of the NSF/IPEC/ANSI 363-2016 US National standard, then the audit time would be expected to be like a combined ISO 9001 and EXCiPACT GMP/GDP Standard audit.

For scope extension, the minimum additional duration should be recalculated after considering the complexity of the added activity.

Deviations in audit durations

The minimum audit durations in 9.1.4.1 identify a starting point which should be adjusted for any special attributes of the organisation and/or system to be audited.

The following factors, and any other as identified as relevant to the organisation and its activities, should be considered, and used to increase the allocated audit time (non-exhaustive):

- complexity of logistics (e.g., involving more than one location),
- staff speaking more than one language, where translators are required or auditors are unable to audit independently,
- complexity and quantity of manufacturing processes, technologies,
- quantity of product groups/families of different types,
- size and dispersion of the site,
- older sites, difficult material flow,
- time consuming access procedures to high-risk areas,
- number of non-conformances recorded in any previous evaluation,
- difficulties experienced during previous evaluations,
- any outsourcing within the scope of certification.

The above points for deviations in the audit duration are indicative and do not cover all situations and all attributes of the specific organisation's system, processes and products or services that should be considered when determining audit time.

Bibliography

No additional bibliography

Appendix 1 Definitions

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

1. **Acceptance criteria**: Numerical limits, ranges, or other suitable measures of acceptance for test results [Q7]
2. **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. [IPEC]
3. **Adequate**: Sufficient, although not necessarily the most or the best.
4. **Appropriate**: A quality of being sufficient to meet the requirements.
5. **Audit team leader**: A qualified individual who organises, coordinates, and is qualified to conduct audits to the GMP or GDP Annexes as applicable.
6. **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.
7. **Batch number (Lot Number)**: A unique combination of numbers, letters and/or symbols that identifies a batch (or lot) and from which the production and distribution history can be determined. [Q7]
8. **Batch process**: A process that produces the excipient from a discrete supply of raw materials that is present before the completion of the reaction. [Q7]
9. **Batch record**: Documents that provide a history of the manufacture of a batch of excipient. [IPEC PQG GMP]

10. **Broker / brokering**: Brokers resell excipients without conducting physical handling of the product such as warehousing, transport, repackaging etc. [IPEC GDP]
11. **Bulk excipient**: Excipient in any transportation or storage equipment (tanks, silos, ISO-Containers, tank/silo trucks etc.) to be filled/ repackaged into others (tanks, silos, drums, bags, containers etc.).
12. **Certificate of analysis (CoA)**: A document listing the test methods, specification, and results of testing a representative sample from the batch to be delivered. [IPEC]
13. **Change**: anything that alters an excipient's physical, chemical and/or microbiological characteristics from the norm, or that is likely to alter the excipient performance in the dosage form.
14. **Change control**: A process used for management review of proposed changes that may impact the quality or regulatory conformance of the excipient. [IPEC]
15. **Competency**: The demonstrated personal attributes and demonstrated ability to apply knowledge and skills. [ISO 19011:2002].
16. **Component**: Any material present in the excipient that arises as a consequence of the raw materials and/or manufacturing process. [IPEC]
17. **Computer system**: A group of hardware components and associated software designed and assembled to perform a specific function or group of functions. [IPEC]
18. **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. [IPEC]
19. **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. [IPEC]
20. **Continual improvement**: Recurring activity to increase the ability to fulfil requirements. [IPEC]
21. **Continuous process**: A process that continually produces material from a continuing supply of raw material. [IPEC]
22. **Contract**: Business agreement for supply of goods or performance of work at a specified price. [WHO GTDP]
23. **Corrective action**: Action 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. [IPEC]

24. **Critical**: A process step, process condition, test requirement or other relevant parameter or item that must be controlled within predetermined criteria to ensure that the excipient meets its specification. [IPEC]
25. **Cross-contamination**: Contamination of a material or product with another material or product. [Q7]
26. **Customer**: The organisation receiving the excipient once it has left the control of the excipient manufacturer; includes brokers, agents and users. [IPEC]
27. **Deviation**: Departure from an approved instruction or established standard. [Q7]
28. **Distributor(s)**: For this Annex "distributors" includes those parties involved in trade and distribution, (re)processors, (re) packagers, (re) labellers, transport and warehousing companies, forwarding agents, brokers, traders, and suppliers other than the original manufacturer.
29. **Distribution**: The division and movement of excipients from the premises of the manufacturer via distributor(s) to the excipient user.
30. **Documented procedure**: A written procedure meeting the requirements of 4.2.3.
31. **Drug product**: Dosage form intended for use by a patient.
32. **Effectiveness**: An expression of the degree to which activities have produced the effects planned. [IPEC]
33. **Excipient**: Substances other than the API which have been appropriately evaluated for safety and are intentionally included in a drug delivery system. [IPEC]
34. **Expiry (expiration) date**: The date designating the time during which the excipient is expected to remain within specifications and after which it should not be used. [IPEC].
35. **Functionality**: A desirable property of an excipient that aids and/or improves the manufacture, quality, or performance of the drug product. [IPEC]
36. **Good distribution practices (GDP)**: Requirements for the quality system under which drug products and their ingredients are handled and distributed.
37. **Good manufacturing practices (GMP)**: Requirements for the quality system under which drug products and their ingredients are

manufactured. Current Good Manufacturing Practice (cGMP) is the applicable term in the United States. For the purposes of this guide, the terms GMP and cGMP are equivalent. [IPEC]

38. **Good warehousing practices (GWP):** requirements for the quality system under which good practices associated with the receipt, storage, despatch, and transportation of pharmaceutical excipients in the original containers and which are not relabelled
39. **ICH**: International Conference on Harmonisation. [IPEC]
40. **IPEC**: International Pharmaceutical Excipients Council. [IPEC]
41. **IPEC PQG**: International Pharmaceutical Excipients Council and the Pharmaceutical Quality Group. [IPEC]
42. **Impurity**: An undesirable component of an excipient that is present because of the raw materials, excipient manufacturing process, or excipient degradation. Impurities are expected to be controlled at a specified level.
43. **In-process control/testing**: Checks performed in production to monitor and, if appropriate, to adjust the process and/or to ensure that the intermediate or excipient conforms to its specification. [IPEC PQG GMP]
44. **Intermediate**: Material that must undergo further manufacturing steps before it becomes an excipient. [IPEC PQG GMP]
45. **Label**: The display of written, printed, or graphic matter on the Immediate container of the excipient (inactive ingredient) product. [IPEC]
46. **Labelling**: The action involving the selection of the correct label, with the required information, followed by line-clearance and application of the label. [WHO GTDP]
47. **Justified**: A documented explanation.
48. **Lot**: see Batch [IPEC]
49. **Manufacture / manufacturing process**: All operations of receipt of materials, production, packaging, repackaging, labelling, relabelling, quality control, release, storage, and distribution of excipients and related controls. [IPEC PQG GMP].
50. **Material**: A general term used to denote raw materials (starting materials, reagents, and solvents), process aids, intermediates, excipients and packaging and labelling materials. [Q7]
51. **Nonconformity / non-conformance**: A non-fulfilment of requirements.

52. **Nonconforming material**: Material that does not meet the manufacturer's specifications or has not been manufactured according to applicable GMPs [IPEC GDP].
53. **Organisation**: As in ISO 9001:2008, "organisation" is used in this Annex to indicate the entity to which the requirements apply.
54. **Original manufacturer**: Person or company manufacturing a material to the stage at which it is designated as a pharmaceutical starting material. [WHO GTDP]
55. **Packaging material**: A material intended to protect an intermediate or excipient during storage and transport. [IPEC]
56. **Pharmaceutical starting materia**l: A pharmaceutical starting material is an active pharmaceutical ingredient (API), or an excipient intended or designated for use in the production of a pharmaceutical product. [WHO GTDP]
57. **Preventive action**: Action to eliminate the cause of a potential nonconformity or other undesirable potential situation. NOTE – [IPEC] Preventive action is taken to prevent occurrence whereas corrective action is taken to prevent recurrence. [IPEC]
58. **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 recognised source. If no official recognised source is available, the reference standard selected shall be appropriately characterised.
59. **Procedure**: Written, authorised instruction for performing specified operations. (see documented procedure) [IPEC GTDP]
60. **Process**: The combination of operating steps including synthesis, isolation, purification, packaging, etc. that produces the finished excipient. [IPEC]
61. **Production**: Operations involved in the preparation of an excipient from receipt of materials through processing and packaging of the excipient. [IPEC]
62. **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 these standards
63. **Quality assurance**: The sum 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. [IPEC PQG GMP]

64. **Quality control (QC)**: Checking or testing those specifications are met. [IPEC]
65. **Quality critical**: Describes a material, process step or process condition, test requirement or any other relevant parameter that directly influences the quality attributes of the excipient and which must be controlled within predetermined criteria. [IPEC]
66. **Quality management system (QMS)**: A management system that directs and controls how the organisation implements quality policies and achieves quality objectives.
67. **Quality risk management**: A systematic process for the assessment, control, communication, and review of risks to the quality of the excipient across its lifecycle.
68. **Quality system**: See Quality Management System.
69. **Quality unit**: An organisational unit independent of production which fulfils both Quality Assurance and Quality Control responsibilities. This can be in the form of separate QA and QC units or a single individual or group, depending upon the size and structure of the organisation. [IPEC].
70. **Quarantine**: The status of materials isolated physically or by other effective means pending a decision on their subsequent approval or rejection. [IPEC].
71. **Raw material**: A general term used to denote starting materials, reagents and solvents intended for use in the production of intermediates or excipients. [IPEC].
72. **Recall (USA: retrieval)**: A process for withdrawing or removing a pharmaceutical material from the distribution chain because of defects in the materials or complaints of a serious nature. The recall might be initiated by the manufacturer/importer/ distributor or a responsible agency. [WHO GTDP].

    Note: In the USA, the term recall has specific regulatory implications that do not directly apply to excipients. Therefore, the term retrieval is typically used in the USA. In this document "recall" has the same meaning as retrieval.
73. **Record**: 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. [IPEC].
74. **Relabelling**: The process of putting a new label on the material (see also labelling). [WHO GTDP].

75. **Repackaging**: The action of changing the packaging of the material. [WHO GTDP].
76. **Representative sample**: A quantity of the excipient taken according to a prescribed rationale to accurately portray the material being sampled (e.g., a batch).
77. **Reprocessing**: Repetition of an activity that is a normal part of the manufacturing process and that has been documented previously. [IPEC].
78. **Requirements**: The explicit or implicit needs or expectations of the governing standards. [IPEC]
79. **Resources**: suggested definition: Source of supply, support, or aid, especially one that can be readily drawn upon when needed.
80. **Retained sample**: Representative sample of a batch/delivery that is sufficient quantity to perform at least two full quality control analyses and will be kept for a defined period of time. [IPEC].
81. **Retest date**: The date when a material should be re-examined to ensure that it is still suitable for use. [IPEC].
82. **Retest/re-evaluation interval**: The duration, normally expressed in months or years, from the date of manufacture, throughout which the excipient should continue to conform to the specification, and after which should be tested to confirm it continues to meet the specification. [IPEC].
83. **Reworking**: Subjecting previously processed material that did not conform to standards or specifications to processing steps that differ from the normal process. [IPEC].
84. **Risk assessment**: A systematic process of organising 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. [IPEC]
85. **Sampling**: Operations designed to obtain a representative portion of a pharmaceutical starting material based on an appropriate statistical procedure, for a defined purpose, e.g., acceptance of consignments, batch release, etc.
86. **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. [IPEC].
87. **Significant change**: Any change that has the potential to alter an excipient's physical, chemical, or microbiological property from the

norm, or that is likely to alter the excipient's performance in the dosage form.

88. **Solvent**: An inorganic or organic liquid used as a vehicle for the presentation of solutions or suspensions in the manufacture of an excipient. [IPEC].
89. **Specification**: A list of tests, references to analytical procedures and appropriate acceptance criteria that are numerical limits, ranges or other criteria for the tests described for a material, that a material is required to meet. [IPEC].
90. **Stability**: Continued conformance of the excipient to its specifications. [IPEC].
91. **State of control**: A condition in which the set of controls consistently provides assurance of continued process performance and product quality. [IPEC].
92. **Subcontractor**: Third party for outsourced work or services which contribute in whole or in part to the manufacture of excipients.
93. **Supplier**: Person or company providing pharmaceutical starting materials on request. Suppliers may be distributors, manufacturers, traders, etc.
94. **Supply chain**: For the purpose of standards, supply chain is defined as all steps in the entire chain of distribution starting from the point at which an excipient is transferred outside the control of the original manufacturer's material management system downstream to the final user of the excipient.
95. **Top management**: Person or group of people who direct and control an organisation at the highest level. The highest level can either be at the site or corporate level and will depend on the way that the quality management system is organised. [IPEC]
96. **Traceability**: Ability to determine the history, application or location that is under consideration, for example, origin on materials and parts, processing history or distribution of the product after delivery. [IPEC].
97. **Validation**: A documented programme that provides a high degree of assurance that a specific product, method, procedure (i.e., cleaning) or system will consistently produce a result that meets predetermined acceptance criteria. [IPEC].
98. **Verification**: The application of methods, procedures, tests, and other evaluations, in addition to monitoring, to determine compliance with the GMP principles. [IPEC]

Appendix 2 References

The following documents were used in the creation of these standards and provide detailed technical information:

- European Commission, EudraLex. The Rules Governing Medicinal Products in the European Union Volume 4 Good Manufacturing Practice Medicinal Products for Human and Veterinary Use Part II: Basic Requirements for Active Substances used as Starting Materials[8]
- ICH Harmonised Tripartite Guideline, *Q6A: Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances,* November 1999[9]
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Appendix 3 Acknowledgements

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Individual Acknowledgements – 2012 Edition

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Note: affiliations correct at time of original publication in 2012.

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2017 Edition

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Notes

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