international excipients certification

EXCIPACT ™

Minimising the risks, maximising the benefits

Certification Standards for Pharmaceutical Excipients: Good Manufacturing practices Good Distribution Practices

Requirements for Auditor Competency and 3rd Party Audit Organisations providing Certification

Prepared by:

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Background & Introduction

The safety of medicines for patients is paramount to all those involved in the supply chain, viz., the pharmaceutical industry, suppliers of raw materials, national and regional health care agencies, care givers and regulators. To assure the quality of medicines produced, risks in the supply chain need to be evaluated and minimized, and this includes not only active pharmaceutical ingredients (APIs) but also pharmaceutical excipients.

There are a great many different excipients used in medicines and on average over 80% of the volume of each medicinal product are excipients. The pharmaceutical excipient market value is estimated to be € 3 bn., or 0.5 % of the total pharmaceutical market according to industry experts. Few excipients are manufactured solely for pharmaceutical use; most are made for other markets, such as food and cosmetics.

With proposed legislation requiring GMP and GDP for excipients in Europe and the USA, excipient suppliers will be faced with an avalanche of customer and customer-led 3rd party audits to ensure they and their products meet these new requirements. Excipient suppliers, distributors and the pharmaceutical industry are committed to the supply and use of high quality excipients throughout the supply chain and aim to control this by self-regulation.

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) have worked together since 2008 on the development of a certification scheme for excipients suppliers – now known as **EXCIPACT ™**.

These parties are in agreement that an international pharmaceutical excipient good manufacturing practice (GMP) and good distribution practice (GDP) certification scheme will help to ensure the safety of pharmaceutical excipients throughout the supply chain, especially where certification is based on the IPEC-PQG GMP and the IPEC GDP Guides..

The **EXCIPACT ™** scheme provides for an independent certification of manufacturers and suppliers of excipients as a means of ensuring patient safety, improving assurance of supplier quality, while minimizing the overall supply chain costs. At the outset, the Excipact ™ Project Global Steering Committee set the following principles and deliverables for the various project teams:

Key project principles:

- *"International"*: an excipient manufacturer's certification should have the same acceptance and value anywhere in the world.
- *"Inclusivity"*: The scheme should provide quality standards and be applicable to as many excipients as possible.
- *"Accessibility"*: The scheme should be accessible from as many 3rd party organizations as possible.
- *"Evolution not revolution"*: Existing best practices, guides and standards should be utilised and adapted wherever possible.
- *"Simplicity"*: The overall scheme should be as simple as possible.

Key deliverables:

- GMP and GDP standards suitable for 3rd party auditing
- Definition of auditor competency for the delivery of the scheme
- Certification scheme rules for 3rd party audit organisations
- Publication, communication and ongoing maintenance of the schemes, standards and guides developed

EXCIPACT ™ - Current Status

The EXCIPACT ™ project teams have drafted the audit standards, auditor competency and 3rd party audit organisation requirements. This edition has been updated following

membership comment and feedback. The purpose of this edition is to allow for a review of the document by stakeholders and any others with an interest, prior to finalisation and implementation.

Acknowledgements

Excipact ™ is the result of a huge amount of effort and commitment from a large team of people spanning two continents and many countries. These individuals are members of the partner organisations that comprise Excipact ™ and without which this standard could not have been prepared.

European Fine Chemicals Group (EFCG)

The European Fine Chemicals Group - a sector group of CEFIC, the European Chemicals Industry Council - was formed in 2004 to be the forum, the focus and the voice for European Fine Chemical Manufacturers. The issues affecting its members' competitiveness drive EFCG. One such issue is the need for certifiable, enforceable, adequate and appropriate quality standards for pharmaceutical excipients destined for use in European medicines.

For further information visit www.efcg.cefic.org

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 companies many of which are small and medium sized enterprises. Members service a very wide range of industries and meet the manufacturing 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)

IPEC is an international industry association formed in 1991 by manufacturers and end-users of excipients. It is an association comprising three regional pharmaceutical excipient industry associations covering the United States, Europe and Japan (which are known respectively as IPEC-Americas, IPEC Europe and JPEC). 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 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.

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. The group has since expanded, and 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.

For further information visit www.pqg.org

IPEC and PQG greatly appreciate and acknowledge the many hours of hard work the following individuals devoted to creating this Guide and the generous support provided by their employers:

Global Steering Committee

Auditor Competency Team

Communications Team

GMP Annex Team

GDP Annex Team

3rd Party Audit Organisation Requirements Team

Review and Proofing Team

Excipact ™ Realisation Teams

Legal Team

Business Planning Team

Communications Team

3rd Party Audit Organisations Team

Stakeholder Management Team

Details to appear later

General Introduction

As of the date of preparation of these Excipact ™ Standards, Good Manufacturing practice (GMP) is not mandated in law in either Europe or the USA for ingredients used in the manufacture of pharmaceuticals. Excipients have no such legal requirement. Yet excipients may pose a hazard to the end 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 recent events with fraudulent claims of pharmaceutical raw material purity have resulted in so many tragedies.

These tragedies have taught us that it is not enough to apply standards only to the manufacture of the excipient. The distribution of the excipient must also be included. Excipient quality can be better assured if all steps in the supply chain, from manufacturer through to user, adopt suitable standards that are capable of independent verification – i.e. Good Distribution Practices (GDP). Patients can be as much at risk from failures in the supply chain as from failures in manufacture, no matter how caused.

Legislators and regulatory authorities in both Europe and the USA continue to address the weaknesses in the application of GMP and GDP to pharmaceutical excipients so as to minimise patient risk. The FDA has clearly stated that they expect each drug product manufacturer to have physically audited **every** API and excipient supplier they use. There are similar moves in place in Europe where similar requirements are proposed. Such requirements, even justified, pose an administrative burden for excipient users and their suppliers alike. How to resource and find time to conduct all these audits? Some excipient supplier sites could be asked to host hundreds of audits as a result of these initiatives. In recognition of these issues the authorities have clearly stated that the drug product manufacturer can utilise 3rd party audit organisations to perform the audits. Thus a 3rd party audit organisation could perform the audit reducing the burden in time and resources for both excipient user and excipient supplier. But for such 3rd party audit organisations to be accepted within this industry both the standard used to assess excipient suppliers and the competency of their auditors must be addressed.

Many excipient suppliers are already registered to the Quality Management System standard, ISO 9001 and this provides an excellent framework to build and develop systems suitable for the supply of pharmaceutical excipients. This is the basis for the Excipact ™ standards by providing two annexes to ISO 9001 to cover both GMP and GDP requirements. Thus excipient manufacturers would be assessed to ISO 9001 and the Excipact ™ GMP annex together, whereas distributors would be assessed to ISO 9001 and the Excipact ™ GDP Annex together. If an excipient supplier conducted both manufacturing and distribution activities they could be assessed to both the GMP and GDP Annexes.

The remaining sections of Excipact ™ cover the requirements for 3rd party audit organisations for auditor competency and for quality system requirements for these organisations. The former is based on ISO 19011, Guidelines for Quality or Environmental Management System Auditing, whereas the latter is based on ISO 17021, Conformity assessment -- Requirements for bodies providing audit and certification of management systems.

Together these standards will ensure pharmaceutical excipient suppliers implement best practices to assure excipient safety and that 3rd party audit organisations can provide a credible service to the pharmaceutical industry and their regulatory authorities.

The Excipact ™ international pharmaceutical excipient GMP and GDP certification scheme will provide manufacturers, suppliers and users of excipients with additional confidence that suppliers of these critical components of drug products are safe to use.

Foreword to this Annex

Many excipient manufacturers and distributors are already registered to ISO 9001, "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 and to the requirements for GMP for pharmaceutical excipients. This annex to ISO 9001:2008 is based on the Joint IPEC-PQG Good Manufacturing Practices Guide for Pharmaceutical Excipients 2006. The guidance ("how to do") in that document has been converted to an auditable standard ("what to do") and then the parts already covered by ISO 9001:2008 removed. This annex is the result.

Organisations that manufacture and distribute excipients can opt 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 9001:2008 and the details are the GMP requirements:

Texts in Bold are ISO 9001 Headings

Standard Texts are GMP requirements
Italicised texts are taken directly from ISO 9001:2008 to provide context to the Annex statements immediately following.

For full comprehension this annex should be read in conjunction with ISO 9001:2008. A copy of that standard is not included herein for copyright and licensing reasons.

0 Introduction

This document is an annex to ISO 9001:2008. Organisations requiring certification to this Annex shall hold a current ISO 9001 certificate. For organisations not holding a current ISO 9001 certificate and for recertification, assessment against the requirements of this annex and ISO 9001 may be conducted simultaneously.

0.1 General

Excipient manufacture shall be carried out in accordance with the 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 pharmacopoeial specification (if existing for the specific excipient) and/or appropriate regulatory requirements and is manufactured, repackaged, and handled in accordance with excipient GMPs (e.g. Excipact ™, IPEC-PQG Excipient GMP, USP <1078>).

This document includes additional requirements that support the application of GMP to the manufacture of excipients. The section headings are consistent with those in ISO 9001:2008. Where 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 6.2.2, where the list starts with” f)”.

0.2 Process approach

No additional requirements to ISO 9001.

0.3 Relationship with ISO 9004

No additional requirements to ISO 9001.

0.4 Compatibility with other management systems

No additional requirements to ISO 9001.

1 Scope

1.1 General

In this Annex the term “if/as applicable” is used several times, when a requirement is qualified by this phrase, it is deemed to be “applicable” unless the organization has a documented risk assessment which concludes that it is not applicable. This process shall also be followed where operations covered in this Annex are not carried out by the organization (outsourced).

Purpose and Scope

The scope of this Annex is the addition of GMP requirements for excipients to ISO 9001:2008 requirements. These principles are to be applied from the point in the manufacturing process where GMP has been determined to begin (see 4.2.2 e).

The Annex and its Use

For guidance on the requirements in this annex consult the IPEC-PQG Good Manufacturing Practices Guide for Pharmaceutical Excipients 2006.

1.2 Application

This Annex includes requirements additional to those for ISO 9001:2008 certification purposes and enables organizations to demonstrate conformity with GMP for the manufacture of excipients.

2 Normative references

ISO 9001:2008, *Quality Management Systems - Requirements*

3 Terms and definitions

See section "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 Quality Management System

4.1 General requirements

Where manufacturing, testing or other operations that could affect excipient quality are outsourced, the organization shall demonstrate that the applicable GMP principles are applied to those operations in accordance with this Annex (see 7.4.1).

4.2 Documentation requirements

4.2.1 General

The quality management system documentation shall include:

e) the organization's overall intentions and approach to GMP
f) documented procedures required for conformance to this Annex
g) a documented risk assessment that defines and justifies when the "as applicable" clauses in this Annex are not implemented.

4.2.2 Quality manual

The organization shall establish and maintain a quality manual that includes or references:

d) a definition of the extent to which this Annex applies to its quality management system and its business processes, and
e) identification and justification of the point at which GMP applies to each manufacturing process.

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

4.2.3 Control of documents

Documents that impact product quality shall have a defined owner. The department with the responsibility for issuing documents shall be identified.

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

Note: The Quality Unit may delegate this responsibility, unless otherwise noted herein, if appropriate controls are in place and are documented (see 5.5.1).

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

4.2.4 Control of records

Records shall include pertinent subcontractor results and reports.

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.

Quality records shall be kept for a defined period. This period shall be appropriate to the excipient and its expiry date or retest interval.

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 COAs.

4.3 Change Control

There shall be a documented procedure for the evaluation and approval of changes that may impact the quality of the excipient. Evaluation and approval of changes shall occur prior to the implementation. The Quality unit, independent from production 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 to customers and, as applicable, regulatory authorities (see 7.2.3).

Note: For Guidance refer to the IPEC Americas Significant Change Guide:

The responsibilities and requirements for evaluating, managing, implementing change and maintaining records (see 4.2.4) shall be described in a documented procedure.

5. Management responsibility

5.1 Management commitment

Top management shall provide evidence of its commitment to the development and implementation of the quality management system and continually improving its effectiveness by:

f) ensuring that GMP objectives are established, and
g) communicating to the organization the importance of conforming to GMP.

5.2 Customer focus

Top management shall ensure that customer requirements related to GMP for pharmaceutical excipients are determined, agreed with the customer and met.

The organization shall permit audits to assess the continued effectiveness of its quality management system, records, manufacturing processes, buildings and facilities.

5.3 Quality policy

Top management shall ensure that the quality policy:

f) includes a commitment to comply with GMP requirements.

5.4 Planning

5.4.1 Quality objectives

Top management shall set objectives for adherence to GMP.

5.4.2 Quality Management system planning

No additional requirements to ISO 9001.

5.5 Responsibility, authority and communication

5.5.1 Responsibility and authority

A quality unit independent from production shall be responsible at a minimum:

- 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 any deviations have been fully investigated
- ensuring corrective and preventive actions are implemented
- approving significant changes to quality critical equipment, processes, specifications, procedures, and test methods (see 4.3),
- investigating failures and complaints
- approving or rejecting the excipient if it is manufactured, processed, packaged, or held under contract by another company, and
- developing and implementing an internal audit program,
- ensuring that providers of outsourced services have agreed to comply with the relevant sections of the Annex.

The Quality Unit may delegate some of these activities 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.

5.5.2 Management representative

No additional requirements to ISO 9001.

5.5.3 Internal communication

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

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.

5.6 Management review

5.6.1 General

No additional requirements to ISO 9001.

5.6.2 Review input

No additional requirements to ISO 9001.

5.6.3 Review output

No additional requirements to ISO 9001.

6 Resource management

6.1 Provision of resources

The organization shall determine and provide the resources needed:

c) to meet the GMP requirements in this Annex which they have determined to be applicable.

6.2 Human resources

6.2.1 General

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

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.

6.2.2 Competence, training and awareness

The organization shall:

f) ensure training, including GMP as it relates to the employee's function, is conducted by qualified individuals,
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 product 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, and
h) ensure GMP refresher training is conducted periodically

6.2.3 Personnel Hygiene

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

a) Personal protective attire and equipment,
b) Removal of loose items, including those in pockets,
c) Prevention of unauthorized access to designated areas (see 6.3),
d) Restriction of any person with an apparent illness or open lesions,
e) Restriction of the storage and use of food, drink, personal medication, tobacco products or similar items.

The organisation shall implement procedures to control the identified risks.

6.3 Infrastructure

The infrastructure shall be designed, operated, cleaned and maintained to avoid contamination and mix-ups of raw materials, intermediates and the excipient. Where the infrastructure is critical to excipient quality, the controls shall be documented. There shall be controls to ensure that defective equipment shall not be used.

Storage containers shall be identified and marked with their contents.

Equipment 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.

Production processes associated with highly sensitizing or toxic materials shall be in equipment separate from that used for excipients, unless measures to prevent cross-contamination have been implemented and the effectiveness of these measures have been demonstrated.

Process materials which are intended to come into contact with the excipient shall be controlled to ensure that they are appropriate for the intended use.

Note: Process materials can include compressed air, inert gases, lubricants, steam additives, filter media, etc.

Computerized systems that may impact upon excipient quality shall have sufficient controls for operation, maintenance, back-up or archiving, and include measures to prevent unauthorized access or changes to software, hardware or data.

Water, where used in contact with excipients shall conform to written specifications and be monitored to be of a suitable quality for its intended use. Unless otherwise justified, water shall, at a minimum meet WHO guidelines for drinking (potable) water quality. Product contact water shall be distributed in such a manner so as to prevent contamination entering or backflows in the system.

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

6.4 Work environment

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

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

a) Air handling systems,
b) Special environments,
c) Cleanliness and sanitary conditions,
d) Waste segregation and disposal,
e) Pest control,
f) Personnel hygiene.

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

7 Product realization

7.1 Planning of product realization

In planning product realization, the organization shall determine the following, as appropriate:

e) documented testing programs for quality critical materials and excipients that include appropriate specifications, sampling plans, test and release procedures,
f) environmental and hygiene control programs to minimize risks of contamination of the excipient,
g) documented procedures describing activities relating to the storage and distribution of excipients

7.2 Customer-related processes

7.2.1 Determination of requirements related to the product

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

7.2.2 Review of requirements related to the product

No additional requirements to ISO 9001.

7.2.3 Customer communication

The organization shall determine and implement effective arrangements for communicating with customers in relation to:

d) significant changes. (See also 4.3 and 7.2.1)
e) critical deviations which become known after delivery of the excipient (see 7.2.1 and 7.2.3).

Certificates of Analysis, which are traceable to the original manufacturers 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.

If production of the excipient is outsourced then this shall be communicated to the customer.

7.3 Design and development

The extent of conformance to this Annex for development batches of excipients shall be communicated to the customer. See section 7.2.1.

7.3.1 Design and development planning

No additional requirements to ISO 9001.

7.3.2 Design and development inputs

No additional requirements to ISO 9001.

7.3.3 Design and development outputs

No additional requirements to ISO 9001.

7.3.4 Design and development review

No additional requirements to ISO 9001.

7.3.5 Design and development verification

No additional requirements to ISO 9001.

7.3.6 Design and development validation

No additional requirements to ISO 9001.

7.3.7 Control of design and development changes

No additional requirements to ISO 9001.

7.4 Purchasing

7.4.1 Purchasing process

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

The organization shall require that contract manufacturers or laboratories adhere to the relevant sections of this Annex (See 4.1).

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.

7.4.2 Purchasing information

The organization shall require that it is notified by its suppliers of any subcontracting or other significant changes to materials that may potentially impact excipient quality.

7.4.3 Verification of purchased product

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, 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 (see 8.2.3).

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

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

7.5 Production and service provision

7.5.1 Control of production and service provision

Controlled conditions shall include, as applicable:

a) *The availability of information that specifies the characteristics of the product,*
No additional requirements to ISO 9001,

b) *The availability of work instructions, as necessary,*
For batch processes documented instructions shall be issued to the production area. For continuous processes, there shall be a defined process and records shall be available.

Records for both batch and continuous processing, where critical to excipient quality shall include:

- date/time each step was completed or date/time log of key parameters,
- identification of persons performing and directly supervising or checking each significant step, 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, and
- results of final product inspection.

and as applicable:

- the quantity produced for the defined batch and a statement of the percentage of theoretical yield,
- inspection of the packaging and labelling area before and after use, labelling control records to ensure the correct label is applied to all containers,
- 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 and reused they shall be controlled to ensure that they meet specifications appropriate for their reuse.
The use of mother liquors or filtrates containing recoverable amounts of excipient, reactants or intermediates shall be documented and records maintained to enable traceability.

c) *The use of suitable equipment,*

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

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

For continuous processing the frequency of equipment cleaning shall be determined by the organisation and justified.

d) *The availability and use of monitoring and measuring equipment,*
No additional requirements to ISO 9001.

e) *The implementation of monitoring and measurement,*
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.

f) *The implementation of product release, delivery and post-delivery activities,*
No additional requirements to ISO 9001.

7.5.2 Validation of processes for production and service provision

The consistent operation of the excipient manufacturing process shall be demonstrated.

Where the intent of blending or mixing is to ensure final batch uniformity, it shall be demonstrated that such processing achieves a state of homogeneity.

7.5.3 Identification and traceability

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

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

Excipient labels shall include:

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

7.5.4 Customer property

No additional requirements to ISO 9001.

7.5.5 Preservation of product

Records of storage conditions shall be maintained monitored and recorded if they are critical for the maintenance of raw material, intermediate or excipient quality characteristics. Storage and handling procedures shall be defined in order to protect containers 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 period.

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

For bulk transport in non-dedicated equipment, verified cleaning procedures shall be applied between loadings, and a list of restricted and/or allowed previous cargoes shall be supplied to the transport companies. Records of cleaning shall be retained.

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

An excipient packaging system shall include the following features:

a) written packaging specifications,
b) containers that do not interact with or contaminate the excipient
c) tamper evident seals, and
d) where containers are to be re-used for re-packaging, verified cleaning procedures including means of removing previous labels shall be applied. Records of cleaning shall be retained.

Distribution records shall be retained to enable retrieval of a batch of excipient.

7.6 Control of monitoring and measuring equipment

No additional requirements to ISO 9001.

8 Measurement, analysis and improvement

8.1 General

No additional requirements to ISO 9001.

8.2 Monitoring and measurement

8.2.1 Customer satisfaction

No additional requirements to ISO 9001.

8.2.2 Internal audit

The organization shall conduct internal audits at planned intervals to determine whether the quality management system:

c) conforms to the requirements of this annex.

8.2.3 Monitoring and measurement of processes

No additional requirements to ISO 9001.

8.2.4 Monitoring and measurement of product

Test methods shall be 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,
- responsibility for monitoring those 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:
      - identity of the sample,
      - test method used,
      - raw data including sample preparation,
      - calculations performed,
      - test results and how they compare with established specifications, and
      - 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 proper 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 test results, is evaluated prior to release of the finished excipient. The Quality Unit shall be responsible for the release of the finished excipient.

Note: For excipients produced by continuous processes 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.

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
ii. The retention period shall be justified and based on the expiry or re-evaluation date.
iii. Shall be stored in a secured location, readily retrievable and in conditions consistent with the recommended storage conditions for the finished excipient
iv. The sample size shall be at least twice the amount required to perform complete specification testing.

e) preparation and issue of certificates of analysis,
f) the tests and limits for impurities,
   i. Excipient manufacturers shall identify and set appropriate limits for known impurities,
g) an evaluation of excipient stability,
   i. The organization shall evaluate excipient stability based on historic data or specific studies. The organization shall define and justify an expiry or retest period and ensure this is communicated to the customer.

8.3 Control of non conforming product

Where applicable, the organization shall deal with nonconforming product by 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 review of the risk to excipient quality.
   As applicable, when performing the risk assessment, consideration shall be given to:
   - new impurities that may be introduced as a result 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, and
   - performance of the excipient
g) Batches shall not be blended with other batches for the purpose of hiding adulterated or non-conforming excipients.

Records of reprocessing and reworking activities shall be retained.

There shall be a 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...

In case of a product non-conformance, an investigation shall be performed to establish whether any other batches are also affected.

Returned excipients shall be quarantined until an evaluation of their quality has been completed by the Quality Unit(s). Records shall include the reason for return and the decision made as to the final disposition.

8.4 Analysis of data

No additional requirements to ISO 9001.

8.5 Improvement

8.5.1 Continual improvement

No additional requirements to ISO 9001.

8.5.2 Corrective action

No additional requirements to ISO 9001.

8.5.3 Preventive action

No additional requirements to ISO 9001.

Definitions and Glossary

A fully set of definitions and glossary will be added in later versions

For more definitions see the Joint IPEC-PQG Good Manufacturing Practices Guide for Pharmaceutical Excipients 2006 and section 3 of ISO 9001:2008.

Organization

As in ISO 9001:2008, “organization” is used in this Annex to indicate the entity to which the requirements apply.

Quality Document

Any document such as a policy, procedure, instruction, form or record that is used in support of the excipient Quality Management / GMP system.

Quality Unit (ref: ICH Q7)

An organizational unit independent of production which fulfils both Quality Assurance and Quality Control responsibilities. This may be in the form of separate QA and QC Units, a single individual (or group), depending on the size and structure of the organization.

References

IPEC Good Distribution Practices Guide for Pharmaceutical Excipients 2006

IPEC Americas Significant Change Guide Version 2 2009

IPEC Stability Program Guide 2010

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

[Others to be added]
<1078>
WHO

Foreword to this Annex

Many excipient manufacturers and distributors are already registered to ISO 9001, "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 and to the requirements for GDP for pharmaceutical excipients. This annex to ISO 9001:2008 is based on the IPEC Good Distribution Practices Guide for Pharmaceutical Excipients 2006. The guidance ("how to do") in that document has been converted to an auditable standard ("what to do") and then the parts already covered by ISO 9001:2008 removed. This annex is the result.

Organisations that manufacture and distribute excipients can opt to be certified 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 9001:2008 and the details are the GDP requirements:

Texts in Bold are ISO 9001 Headings

Standard Texts are GDP requirements
Italicised text is taken directly from ISO 9001:2008 to provide context to the Annex statements immediately following.

For full comprehension this annex should be read in conjunction with ISO 9001:2008. A copy of that standard is not included herein for copyright and licensing reasons.

0 Introduction

This document is an annex to ISO 9001:2008. Organisations requiring certification to this Annex shall hold a current ISO 9001 certificate. Assessment against the requirements of this annex and ISO 9001 may be conducted simultaneously.

0.1 General

Excipient distribution shall be carried out in accordance with Good Distribution Practices (GDP) consistent with this Annex. The objective of excipient GDP is to maintain pharmaceutical excipient quality and consistency, whilst ensuring traceability of the material throughout the entire supply chain.

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

There shall be no upgrading of non-pharmaceutical grade product to pharmaceutical grade only on the basis of analytical testing and/or re-packaging. An excipient can only be pharmaceutical grade when it is in compliance with pharmacopoeial specification (if existing for the specific excipient) and/or appropriate regulatory requirements and is manufactured, repackaged, and handled in accordance with excipient GMPs (e.g. Excipact ™, IPEC-PQG Excipient GMP, USP <1078>).

Throughout the document there are parentheses in the form [ref] referring to sections in the IPEC Good Distribution Practices Guide for Pharmaceutical Excipients.

This document includes additional requirements that support the application of GDP to the supply of excipients. The section headings are consistent with those in ISO 9001:2008. Where 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 6.2.2, where the list starts with" f)".

0.2 Process approach

No additional requirements to ISO 9001.

0.3 Relationship with ISO 9004

No additional requirements to ISO 9001.

0.4 Compatibility with other management systems

No additional requirements to ISO 9001.

1 Scope

1.1 General

In this Annex the term "if/as applicable" is used several times. When a requirement is qualified by this phrase, it is deemed to be "applicable" unless the organization has a documented risk assessment which concludes that it is not applicable. This process shall also be followed where operations covered in this Annex are not carried out by the organization (outsourced).

Note: The "Matrix of Applicability" included as table 1 in the IPEC Good Distribution Practices Guide (GDP) may be used as guidance to decide applicability.

Purpose and Scope

The scope of this Annex is the addition of GDP requirements for excipients to ISO 9001:2008 requirements. These principles are to be applied by any party in the supply chain other than the original manufacturer of the excipients.

The Annex and its Use

The Annex should be used in conjunction with the current IPEC Good Distribution Practices Guide for Pharmaceutical Excipients which provides detailed guidance.

1.2 Application

This Annex includes requirements additional to those required for ISO 9001:2008 certification purposes and enables organizations to demonstrate conformity with GDP for excipients for the:

- transportation of bulk or packed excipients
- warehousing (storage of packed excipients)
- brokering, trading, and reselling of packed excipients
- packaging, re-packaging and processing
- sampling, testing, and re-testing
- relabeling
- bulk handling and bulk storage

2 Normative references

ISO 9001:2008, *Quality Management Systems - Requirements*

3 Terms and definitions

See section "Definitions and Glossary".

Pharmaceutical excipients

Pharmaceutical excipients are substances other than the Active Pharmaceutical Ingredient (API) which have been appropriately evaluated for safety and are intentionally included in a drug delivery system.

4 Quality management system

4.1 General requirements

Where distribution activities, as noted in 1.2 that could affect excipient quality are outsourced, the organization shall demonstrate that the applicable GDP principles are applied to those operations in accordance with this Annex (see 7.4.1).

4.2 Documentation requirements

4.2.1 General

The Quality Management system documentation shall include:

e) the organization's overall intentions and approach to GDP
f) documented procedures required for conformance to this Annex
g) a documented risk assessment that defines and justifies when the "as applicable" clauses in this Annex are not implemented.

4.2.2 Quality Manual

The organization shall establish and maintain a quality manual that includes or references:

d) a definition of the extent to which this Annex applies to its quality management system and its business processes.

4.2.3 Control of documents

Documents that impact product quality shall have a defined owner. The department with the responsibility for issuing documents shall be identified.

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

Note: The Quality Unit may delegate this responsibility, unless otherwise noted herein if appropriate controls are in place and are documented (see 5.5.1).

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

4.2.4 Control of records

Records shall include pertinent subcontractor results and reports.

Electronic records shall be subject to the same controls as those required or 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 performing the activity and making the entry. Corrections to entries shall be signed or initialled and dated, leaving the original entry legible.

Quality records shall be kept for a defined period. This period shall be appropriate to the excipient and its expiry date or retest interval.

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 COAs. [6.3, 6.4]

4.3 Change Control

There shall be a documented procedure for the evaluation and approval of changes that may impact the quality of the excipient. Evaluation and approval of changes shall occur prior to implementation. The Quality Unit 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, regulatory authorities (see 7.2.3).

Note: For Guidance refer to the IPEC Americas Significant Change Guide:

The responsibilities and requirements for evaluating, managing, implementing change and maintaining records (see 4.2.4) shall be described in a documented procedure.

5. Management responsibility

5.1 Management commitment

Top management shall provide evidence of its commitment to the development and implementation of the quality management system and continually improving its effectiveness by:

f) ensuring that GDP objectives are established, and
g) communicating to the organization the importance of conforming to GDP

5.2 Customer focus

Top management shall ensure that customer requirements related to GDP for pharmaceutical excipients are determined, agreed with the customer and met.

The organization shall permit audits to assess the continued effectiveness of its quality management system, records, excipient handling processes, buildings and facilities.

5.3 Quality Policy

Top management shall ensure that the quality policy:

f) includes a commitment to comply with GDP requirements.

5.4 Planning

5.4.1 Quality objectives

Top management shall set objectives for adherence to GDP.

5.4.2 Quality Management system planning

No additional requirements to ISO 9001.

5.5 Responsibility, authority and communication

5.5.1 Responsibility and authority

A quality unit independent from production shall be responsible at a minimum:

- ensuring quality critical activities are identified and undertaken as defined,
- approving suppliers of excipients, quality critical materials and services,
- reviewing batch records to ensure any deviations are fully investigated
- ensuring corrective and preventive actions are implemented,
- approving or rejecting packaging components and excipients,
- approving significant changes to quality critical equipment, processes, specifications, procedures, and test methods (see 4.3),
- investigating failures and complaints,
- developing and implementing an internal audit program.
- ensuring that providers of outsourced services have agreed to comply with the relevant sections of the Annex.

The Quality Unit may delegate some of these activities 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.

5.5.2 Management representative

No additional requirements to ISO 9001.

5.5.3 Internal communication

GDP and regulatory requirements shall be communicated as appropriate throughout the organization.

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.

5.6 Management review

5.6.1 General

No additional requirements to ISO 9001.

5.6.2 Review input

No additional requirements to ISO 9001.

5.6.3 Review output

No additional requirements to ISO 9001.

6 Resource management

6.1 Provision of resources

The organization shall determine and provide the resources needed:

c) to meet the GDP requirements in this Annex which they have determined to be applicable.

6.2 Human resources

6.2.1 General

Personnel whose role has an impact on excipient quality shall have written job descriptions [2.2].

Records shall be maintained listing the name, address and qualifications of consultants providing advice concerning any aspect of this Quality Management System and the type of service they provide.

6.2.2 Competence, training and awareness

The organization shall:

f) ensure training, including GDP as it relates to the employee's function, is conducted by qualified individuals,
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 customer/patient if an excipient is contaminated,
    iv. potential impact on product quality and use due to departures from specified procedures,
    v. the risk of excipient contamination from deficiencies in personal hygiene, environment conditions,
    vi. the reporting of significant failures and deviations from procedures.
h) ensure GDP refresher training is conducted periodically

6.2.3 Personnel Hygiene

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

a) Personal protective attire and equipment,
b) Removal of loose items, including those in pockets,
c) Prevention of unauthorized access to designated areas (see 6.3),
d) Restriction of any person with an apparent illness or open lesions,
e) Restriction of the storage and use of food, drink, personal medication, tobacco products or similar items.

The organisation shall implement procedures to control the identified risks

6.3 Infrastructure

The infrastructure shall be designed, operated, cleaned and maintained to avoid contamination and mix-ups of the excipient. Where the infrastructure is critical to excipient quality, the controls shall be documented.

There shall be controls to ensure that defective equipment shall not be used. [3.1, 4.2, 4.3, 5.1, 5.7].

Storage containers shall be identified and marked with their contents [5.3, 5.4].

Equipment 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.

Processes associated with highly sensitizing or toxic materials shall be in equipment separate from that used for excipients, unless measures to prevent cross-contamination have been implemented and the effectiveness of these measures have been demonstrated.

Process materials which are intended to come into contact with the excipient shall be controlled to ensure that they are appropriate for the intended use [5.6].

Note: Process materials can include compressed air, inert gases, lubricants, steam additives, filter media, etc.

Computerized systems that may impact upon excipient quality shall have sufficient controls for operation, maintenance, back-up or archiving, and include measures to prevent unauthorized access or changes to software, hardware or data.

Water, where used in contact with excipients shall conform to written specifications and be monitored to be of a suitable quality for its intended use. Unless otherwise justified, water shall, at a minimum meet WHO guidelines for drinking (potable) water quality. Product contact water shall be distributed in such a manner so as to prevent contamination entering, or backflows in the system.

Access to areas of the buildings and facilities designated as limited access areas shall be controlled [3.2].

6.4 Work environment

The work environment shall be managed and controlled to minimize risks of excipient contamination. A documented risk assessment shall be carried out to determine the necessary controls [3.3, 3.4, 3.5, 4.3, 4.11, 4.13., 7.2, and 7.8].

The documented risk assessment shall cover 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.

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

7 Product realization

7.1 Planning of product realization

In planning product realization, the organization shall determine the following, as applicable and appropriate:

e) documented testing programs for quality critical materials that include appropriate specifications, sampling plans, test and release procedures,
f) environmental and hygiene control programs to minimize risks of contamination of the excipient,
g) documented procedures describing activities relating to the storage and distribution of excipients [4.1].

7.2 Customer-related processes

7.2.1 Determination of requirements related to the product

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

7.2.2 Review of requirements related to the product

No additional requirements to ISO 9001.

7.2.3 Customer communication

The organization shall determine and implement effective arrangements for communicating with customers in relation to:

d) significant changes (See also 4.3. and 7.2.1)

e) critical deviations which become known after delivery of the excipient (see 7.2.1 and 7.2.3).

f) 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 [6.6],

g) each batch shipped regarding the original manufacturer and the manufacturing site(s) as well as expiry and/or re-test dates.

Certificates of Analysis that are traceable to the manufacturer's original COA shall be provided for each batch shipped. The original manufacturer's identity and production site shall be communicated to the customer

7.3 Design and development

No additional requirements to ISO 9001.

7.3.1 Design and development planning

No additional requirements to ISO 9001.

7.3.2 Design and development inputs

No additional requirements to ISO 9001.

7.3.3 Design and development outputs

No additional requirements to ISO 9001.

7.3.4 Design and development review

No additional requirements to ISO 9001.

7.3.5 Design and development verification

No additional requirements to ISO 9001.

7.3.6 Design and development validation

No additional requirements to ISO 9001.

7.3.7 Control of design and development changes

No additional requirements to ISO 9001.

7.4 Purchasing

7.4.1 Purchasing process

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

The organization shall require that contract manufacturers or laboratories adhere to the relevant sections of this Annex (See 4.1) [13.1, 13.4, and 13.5]

Where purchased, 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.

7.4.2 Purchasing information

The organization shall require that it is notified by its suppliers of any significant change to the excipient that may impact quality or functionality.

Any GDP or GMP relevant activity outsourced to another party shall be agreed upon in a written contract including the application of the relevant parts of this annex [13.1, 13.4].

7.4.3 Verification of purchased product

Incoming quality critical materials (including pre-printed labels and all excipients) shall be physically or administratively quarantined until they have been tested or otherwise verified and approved for use. Where quarantine is not feasible, the organization shall establish an agreement with the supplier so that they are notified of material that does not meet specification (see 8.2.3).

The organization shall define and document the controls required to verify identity and quality of purchased products [4.1].

Materials which are to be transferred into another container shall be sampled and tested. Key-parameters shall be tested to verify the identity and quality of such material.

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

Materials which are not sampled shall have controls in place to ensure their quality.

Bulk deliveries shall have controls to ensure freedom from contamination.

7.5 Production and service provision

7.5.1 Control of production and service provision

Controlled conditions shall include, as applicable:

a) *The availability of information that specifies the characteristics of the product,*
No additional requirements to ISO 9001.

b) *The availability of work instructions, as necessary,*
For re-packaging and other manufacturing operations written instructions shall be made available to the operator.

Records for these operations shall include:

- date/time each step was completed or date/time log of key parameters,
- identification of persons performing and directly supervising or checking each significant step, 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
- description of sampling performed,
- in-process and laboratory control results,
- labelling control records,

- failures, deviation and their investigations, and
- results of final product inspection.

and as applicable:

- inspection of the packaging and labelling area before and after use, labelling control records to ensure the correct label is applied to all containers.

Records of quality-critical equipment use shall allow the sequence of cleaning, maintenance and operational 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,

c) *The use of suitable equipment,*

The organization shall design and justify equipment cleaning and sanitization procedures and provide evidence of their effectiveness [5.8].

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

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

d) *The availability and use of monitoring and measuring equipment,*
No additional requirements to ISO 9001.

e) *The implementation of monitoring and measurement,*
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. Samples shall not be returned to the batch.

f) *The implementation of product release, delivery and post-delivery activities,*
No additional requirements to ISO 9001.

7.5.2 Validation of processes for production and service provision

Where the intent of blending or mixing is to ensure final batch uniformity, it shall be demonstrated that such processing achieves a state of homogeneity.

7.5.3 Identification and traceability

The original manufacturer, intermediaries and handling operations of the excipient shall always be traceable and the information made available to regulatory authorities and customers, both downstream and upstream [6.5; 7.11].

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

Excipient labels shall include:

a) the name of the excipient and grade if applicable,

b) the organisation's and/or manufacturer's name,
c) the batch number, and
d) any special storage conditions, if applicable.

7.5.4 Customer property

No additional requirements to ISO 9001.

7.5.5 Preservation of product

Records of storage conditions shall be maintained, monitored and recorded if they are critical for the maintenance of raw material, intermediate or excipient quality characteristics. Storage and handling procedures shall be defined in order to protect containers and closures, minimise the risk of contamination, damage or deterioration of the excipient and prevent mix-ups [4.7].

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

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

For bulk transport in non-dedicated equipment, verified cleaning procedures shall be applied between loadings, and a list of restricted and/or allowed previous cargoes shall be supplied to the transport companies [12.7]. Records of cleaning shall be retained.

Steps shall be taken, such as tamper evident seals, to provide evidence of unauthorized access to the materials being transported [12.8].

An excipient packaging system shall include the following features:
a) written packaging specifications,
b) containers that do not interact with or contaminate the excipient,
c) tamper evident seals, and
d) where containers are to be re-used for re-packaging, verified cleaning procedures including means of removing previous labels shall be applied. Records of cleaning shall be retained, [7.7].

Distribution records shall be retained to enable retrieval of a batch of excipient.

7.6 Control of monitoring and measuring equipment

No additional requirements to ISO 9001.

8 Measurement, analysis and improvement

8.1 General

No additional requirements to ISO 9001.

8.2 Monitoring and measurement

8.2.1 Customer satisfaction

No additional requirements to ISO 9001.

8.2.2 Internal audit

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

c) conforms to the requirements of this annex.

8.2.3 Monitoring and measurement of processes

No additional requirements to ISO 9001.

8.2.4 Monitoring and measurement of product

Test methods shall be suitable for their intended purpose.

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

- non-compendial analytical tests shall be demonstrated to be at least equivalent to those in the compendia, and
- the method shall comply with applicable general chapters and notices.
- responsibility for monitoring those 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:
      - identity of the sample,
      - test method used,
      - raw data including sample preparation,
      - calculations performed,
      - test results and how they compare with established specifications, and
      - 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 proper 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 and/or packaging documentation, in addition to the test results, is evaluated prior to release of the finished excipient. The Quality Unit shall be responsible for the release of the finished excipient.

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.

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.
   ii. The retention period shall be justified and based on the expiry or re-evaluation date,
   iii. Shall be stored in a secured location, readily retrievable and in conditions consistent with the recommended storage conditions for the finished excipient
   iv. The sample size shall be at least twice the amount required to perform complete specification testing [7.14].

e) preparation and issue of certificates of analysis,

f) an evaluation of excipient stability,
   i. Where excipients are repackaged there should be documented evidence that their stability has not been adversely affected and specified expiry dates or re-test periods are justified [7.15].

8.3 Control of non conforming product

Where applicable, the organization shall deal with nonconforming product by one or more of the following ways:

e) rejection,
f) downgrading to a grade of lower quality,
g) return of the material to the original manufacturer,
h) disposal,
i) batches shall not be blended with other batches for the purpose of hiding adulterated or non-conforming excipients.

Note: Out-Of-Specification batches may be re-worked or re-processed to meet agreed specifications (for more details see the Excipact ™ GMP standard).

There shall be procedures for the holding, testing, and downgrading of non-conforming excipient.

Customer complaints and information about possible defects should be systematically investigated and documented, based on a written procedure with assigned responsibilities [8].

There shall be a procedure defining how to manage the retrieval of a pharmaceutical excipient. All retrieval processes shall be documented, notified to the original manufacturer and records retained. Retrieved materials shall be identified and quarantined [9].

In case of a product non-conformance, an investigation shall be performed to establish whether any other batches are also affected [8.3].

Returned excipients shall be quarantined until an evaluation of their quality has been completed by the Quality Unit(s). Records shall include the reason for return and the decision made as to the final disposition [11.1, 11.2, and 11.3].

8.4 Analysis of data

No additional requirements to ISO 9001.

8.5 Improvement

8.5.1 Continual improvement

No additional requirements to ISO 9001.

8.5.2 Corrective action

No additional requirements to ISO 9001.

8.5.3 Preventive action

No additional requirements to ISO 9001.

Definitions and Glossary

A fully set of definitions and glossary will be added in later versions

For more details see the IPEC Good Distribution Practices Guide for Pharmaceutical Excipients 2006 as well as Section 3 of ISO 9001:2008.

Distributor(s):
For the purpose of this Annex "distributors" includes those parties involved in trade and distribution, (re)processors, (re)packagers, transport and warehousing companies, forwarding agents, brokers, traders, and suppliers other than the original manufacturer.

Organization
As in ISO 9001:2008, "organization" is used in this Annex to indicate the entity to which the requirements apply.

Original Manufacturer:
Person or company manufacturing a material to the stage at which it is designated a pharmaceutical starting material (see GDP and WHO guides)

Quality Unit (ref: ICH Q7)
An organizational unit independent of production which fulfils both Quality Assurance and Quality Control responsibilities. This may be in the form of separate QA and QC Units, a single individual (or group), depending on the size and structure of the organization.

References

IPEC Good Distribution Practices Guide for Pharmaceutical Excipients 2006

IPEC Americas Significant Change Guide 2009

Joint IPEC-PQG Good Manufacturing Practices Guide for pharmaceutical Excipients 2006

[Others to be added]

Annex to ISO 19011:2002: Additional Requirements for the Qualification of Auditors and Conducting Audits of Excipient Suppliers

Introduction

This document is an annex to ISO 19011, Guidelines for quality and/or environmental management systems auditing, as this is the most appropriate publicly available document and the most commonly used by 3rd party audit organisations. The headings and sections in this document are those of ISO 19011 and any additional text stipulates requirements that need to be implemented along with the ISO 19011 clauses in order to perform Excipact ™ GMP and GDP certification assessments. Although ISO 19011 is written as guidance all 3rd party audit organisations offering Excipact ™ certification will be expected to comply with all clauses, plus those in this section of Excipact ™.

Where a heading or section of ISO 19011 is omitted then there are no additional requirements to those already stipulated in ISO 19011. *Text in italics is a summary of the main features of the relevant clauses in ISO 19011 and is provided as an aid to comprehension of the additional requirements in this annex.*

Thus the requirements in this document will be simple to implement in organisations that are already using ISO 19011 as the basis of their auditing and for defining auditor competency.

These additional requirements have been defined by Excipact ™ so that are able to lead and conduct audits using the definitions of Good Manufacturing Practice (GMP) and Good Distribution Practice (GDP) in the Excipient Certification Scheme. The requirements in this document constitute a definition of auditor competency.

The regulatory authorities who are responsible for the safety of pharmaceuticals have consistently signalled that a suitable 3rd party audit scheme would be acceptable as a means of assuring the quality and GMP requirements of pharmaceutical excipients – but only if the auditors are of a suitable calibre in terms of knowledge, experience and expertise. Thus organisations wishing to offer 3rd party certification based upon audits using the GMP and GDP standards in this scheme will also have to ensure their auditors meet the requirements in this document.

The document defines the requirements to be met by auditors in order for them to conduct audits of manufacturers of excipients according to GMP and audits of distributors/traders of excipients according to GDP. To carry out only GDP audits of distributors/traders of excipients the principles of auditing (section 4) and management of the audit programme (section 5) are the same, but only the general and the GDP related requirements in section 6, section 7 and appendix A need to be met. Section 7.4.4 b) gives the details related to education and experience required for GDP auditors.

The appendix to this document provides guidance on the topics in this document and also sets out the minimum study requirements for excipient auditors. This appendix can be used to develop suitable training programmes to qualify auditors.

The overall arrangements for conducting audits and for delivering certification are covered in the next section of Excipact ™.

Excipact ™ will require all certification bodies to comply with these requirements.

1. Scope

ISO 19011 provides guidance on how to audit an organisations quality or environmental system. It describes the principles of auditing, managing audit programs, and the criteria for auditor competency. In the context of Excipact ™ assessments, it indicates that the auditors should 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 Annexes. In addition, those personnel making the certification decision in the 3rd party audit organisation should also comply with these requirements.

2. Normative references

ISO 19011:2002 Guidelines for quality and /or environmental management system auditing
EU Guide to GMP Part 1 Chapter 4 and 21CFR 211.188

3. Terms and Definitions

The terms and definitions in ISO 19011 apply, as well as the following:

- Excipient
  Substances other than the Active Pharmaceutical Ingredient (API) which have been appropriately evaluated for safety and are intentionally included in a drug delivery system.

- GMP
  GMP is that part of quality assurance which ensures that products are consistently produced and controlled to the quality standard appropriate to their intended use in the pharmaceutical industry and as required by the product specification. The terms "current Good Manufacturing Practices" (cGMP) and "Good Manufacturing Practices" are equivalent.

- GDP
  GDP is that part of quality assurance which ensures that products are consistently handled and controlled during the supply chain from the original manufacturer to the final user according to the quality standards appropriate to their intended use in the pharmaceutical industry and as required by the product specification and other regulatory requirements.

- Substantial Conformance
  The quality system under which the excipient is manufactured is adequate to produce excipients consistent with the Excipact ™ GMP and GDP Annex and ISO 9001:2008 and without undue risk to the health of the consumer.

- Audit Team Leader
  A qualified individual who organizes, coordinates, and is qualified to audit to the GMP or GDP Annex as applicable.

4. Principles of Auditing

Section 4 describes how the organisation adopts the principles of good auditing practice to ensure reliable and consistent audits and audit outcomes. The section describes the prerequisites which shall be implemented to ensure that audits generate relevant conclusions and that different auditors can reach the same conclusions given the same circumstances.

All auditors shall follow and adopt the following principles:

a) Ethical Conduct
- Will not accept any inducements that may affect decision-making.
- Will not disclose any information to a third-party without written authorization.

b) Fair Presentation
No additional requirements

c) Due Professional Care
- Will only undertake assignments for which they are qualified (e.g. GMP, GDP etc)

d) Independence:
- Will have no conflict of interest with the party being audited
    1. No financial incentive
    2. No personal interest
    3. No consulting in the area of the audit within the previous 2 years or the following 2 years
- Will be financially independent of the party being audited
- Will be independent of the organisation being audited

e) Evidence-based Approach
No Additional requirements

5. Managing an Audit Programme

5.1 General

Section 5 defines an audit programme, and goes onto indicate that the audit organisations top management should define who is responsible for managing such programme(s). The audit programme follows the "Plan, Do, Check, Act" approach embodied in ISO 9001 and describes each of these phases.

No Additional requirements

5.2 Audit Programme objectives and extent

The organisation should set objectives and define the scope for the audit programme as a prerequisite for directing audit planning and implementation activities.

5.2.1. The Objectives of an Audit Programme are to:

- Verify conformance of the auditee's quality system to Excipient GMP and/or GDP requirements so as to confirm the excipient is suitable for its intended use in the dosage form (where known).
- Confirm that the site has the ability to consistently produce the intended excipient.

5.2.2. The extent of the Audit Programme shall include:

- All excipients and related operations to be certified.
- The degree of supply chain assessment as indicated in the application scope.
- At least an annual site audit.

5.3 Audit Programme Responsibilities, Resources, and Procedures

The organisation should manage audit programmes by allocating individuals with knowledge and understanding of auditing, management skills and technical and business understanding relevant to the activities to be audited.

5.3.1 Audit Programme Responsibilities

Shall be in conformance with ISO 19011 and this standard

5.3.2 Audit Programme Resources

- Auditors shall meet the requirements of competency set out in Section 7
- The audit team shall have the expertise to properly assess all operations within the scope of the certification.
  - Where the audit is conducted by a sole auditor, that individual shall have the skills to conduct the audit and write the audit report.

5.3.3 Audit Programme Procedures

- The auditee and the auditors shall be notified of the intended auditors prior to the assessment
- Both the auditors and the auditee shall notify the 3rd party audit organisation if there is any conflict of interest in the assignment of these auditors
- If there is any conflict of interest, then other auditors shall be allocated

5.4 Audit Programme implementation

Documented procedures are required to define the audit programme elements.

The guidance in ISO 19011 shall be followed for conducting audits. The formality required will depend upon the size and culture of the auditee.

5.5 Audit Programme records

Records of audit activities should be retained to demonstrate audit programmes have been implemented as intended.

Programme records shall conform to Good Documentation Practices

5.6 Audit Programme monitoring and reviewing

The audit organisation should periodically monitor, review and report to top management, that audit programmes and objectives have been satisfied. Opportunities for improvement of audit programmes should be identified as part of this review process.

The following indicators of non-conformance of the quality system shall be monitored since they may impugn the quality system audit:

- Complaints from customers may be monitored to assess the effectiveness of the quality system
- Adverse findings from Regulatory inspections of the auditee
- Market withdrawal (recall) of an excipient lot or license withdrawal

6. Audit activities

6.1 General

Section 6 describes the core requirements relating to initiating, preparing for and performing the audit, together with post audit process. It also emphasises the importance of effective communication both with the auditee and other audit team members if involved.

No additional requirements.

6.2 Initiating the audit

The Audit team leader should be competent at establishing and implementing an audit programme which should be capable of meeting defined objectives and gains acceptance from the auditee.

6.2.1. The Audit Team Leader shall

- Hold an established qualification of specific GMP and/or GDP audit experience and meet the competency criteria in Section 7 as well as at least one of the following. -
  - be registered as a quality Lead Auditor i.e. by an accredited certification body,
  - be registered 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 audits such as to ISO 9001, ISO 14001 audits, or pharmaceutical or excipient or API GMP/GDP audits

6.2.2. Defining Audit Objectives, Scope, and Criteria

The audit shall evaluate the following:

- GMP where the applicant is a manufacturer
- GDP where the applicant is a distributor or where distribution is within scope
- All operations either on site or outsourced which are performed to produce the excipient from the point where full GMP begins through to storage and shipment of the packaged excipient.

6.2.3. Determining the Feasibility of the Audit

No additional requirements

6.2.4. Selecting the Audit Team

- The scope of the audit shall be used to determine the number of auditors required so that the duration minimizes the impact to site operations (see next section in Excipact ™ for details of audit durations)
- The audit team shall include at least one Excipact ™ qualified auditor meeting the auditor competency criteria in section 7. All members of the audit team shall be Excipact ™ trained pending qualification. There shall be a minimum of one qualified auditor per non-qualified auditor on the team.

6.2.5. Establishing Initial Contact with the Auditee

The audit team leader shall communicate with the site representative concerning:

- Security requirements such as auditor identification, carrying electronic devices including cell phone, and a camera.
- Confirmation of the scope of the audit and any off-site operational activities such as packaging, warehousing, and testing.
- Inquire about the need for the execution of additional confidentiality requirements, in order to establish the ability to take copies of evidence with the auditor, e.g. pictures/images, sample documents

6.3 Conducting document review

The audit team leader shall request the following additional documentation for review prior to the site audit (where available):

- A completed pre-audit questionnaire.
- Flow diagram(s) showing key processes

- List of procedures supporting the GMP/GDP quality system
- Quality Manual for the GMP/GDP quality system and/or Site Master File
- Site map showing the layout and size of the excipient operations conducted at the facility.

6.4 Preparing for the on-site audit activities

6.4.1 Preparing the Audit Plan

No additional requirements

6.4.2 Assigning Work to the Audit Team

No additional requirements

6.4.3 Preparing Work Documents

- Preparation of a checklist is good practice

Note: The IPEC-PQG GMP Excipient Auditing Guide and the IPEC GDP Excipient Auditing Guides are helpful in the development of checklists.

6.5 Conducting on-site audit activities

6.5.1 Conducting the Opening Meeting

The purpose of an opening meeting is:

e) to inform the auditee of the process for discussing audit and agreeing audit findings

f) To seek agreement concerning the members of the organization with whom discussions will be allowed.

6.5.2 Communications During the Audit

No additional requirements

6.5.3 Roles and Responsibilities of Guides and Observers

No additional requirements

6.5.4 Collecting and Verifying Information

No additional requirements

6.5.5 Generating Audit Findings

No additional requirements

6.5.6 Preparing Audit Conclusions

- Audit conclusions should be limited to the type of audit and scope, and shall not include recommendations.

6.5.7 Conducting the Closing Meeting

- Provide a summary of the compliance of site to the Annex and the severity of nonconformities
- Conclusion as to conformance to Excipient GMP and or GDP should be stated as the opinion of the audit team.

6.6 Preparing, approving and distributing the audit report

6.6.1 Preparing the audit report

- The audit report shall clearly describe the scope of activities covered by the audit including excipients and grades as well as operational activities.
- The audit report shall disclose any areas of excipient GMP and/or GDP scope that were not covered.

6.6.2 Approving and distributing the audit report

- The audit report shall be reviewed and approved by the certification body so that a decision on certification can be made (See Scheme Section 9.2.5)
- The auditee should have an opportunity to review the draft report for the accuracy of the report contents, to identify the presence of confidential information that may be unnecessary to support the observations, and to provide a Corrective & Preventive Action plan.

6.7 Completing the audit

- Confidentiality of the audit report shall be protected.

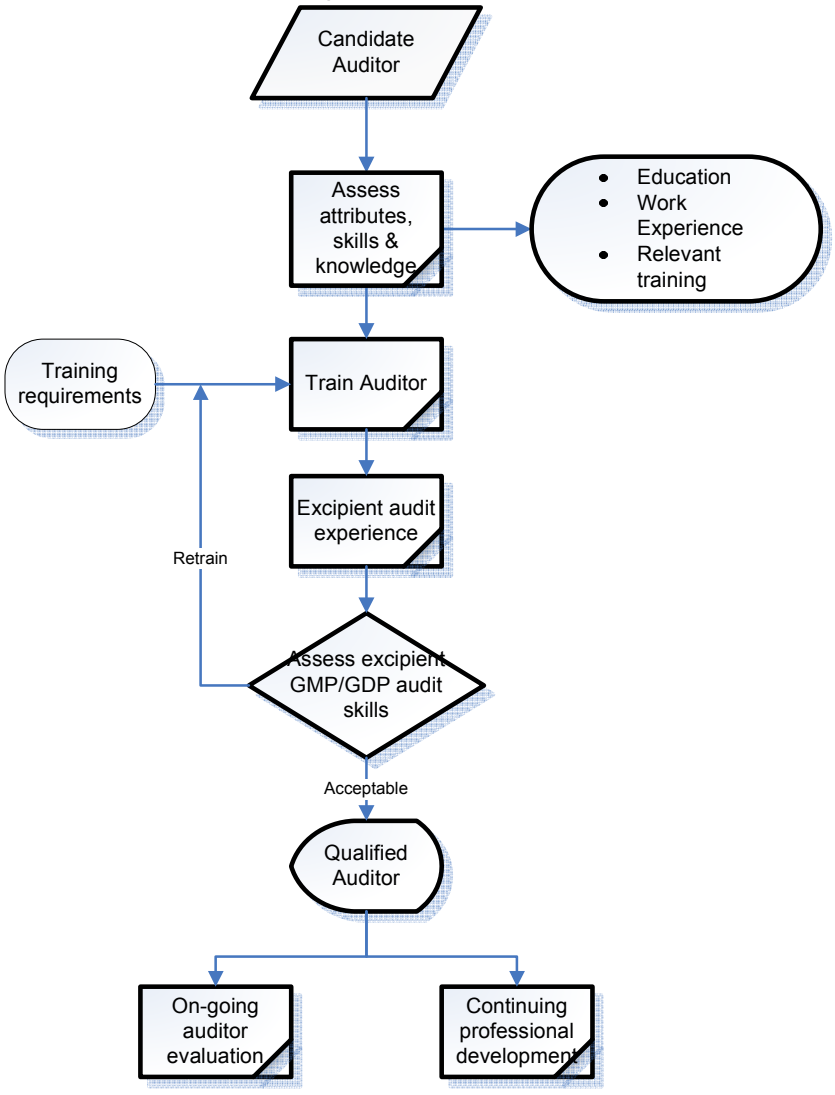
6.8 Conducting audit follow-up

The auditee should be requested to confirm the CAPA plan has been implemented. The status of the CAPAs should be verified no later than the next audit.

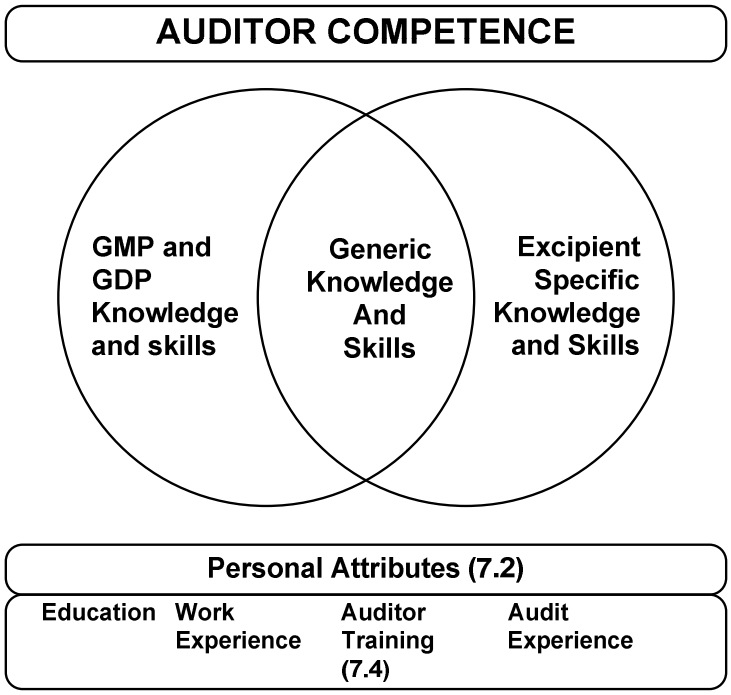
7 Competence and Evaluation of Auditors

7.1 General

This flow diagram illustrates the process for identifying, training and evaluating auditors as well as confirmation of their competence.



Auditor competency is a mixture of knowledge, education, experience and skill. The interrelationship of these attributes in relation to assessing organisations against the GMP /GDP requirements of Excipact ™ is indicated in the following diagram:



Source ISO 19011

7.2 Personal Attributes (refer to Appendix A for further details)

Auditors shall be selected on the basis of having a number of important personal attributes which should enable them to enable to be effective. Such effectiveness shall be periodically reviewed relative to these attributes:

j) Maturity
k) Sound Judgement
l) Integrity
m) Proven ability to put people at ease and understand the auditee's perspective.
n) Proven ability to assure conduct of the audit to the audit schedule and within the scope.

7.3 Knowledge and Skills

7.3.1 Generic Knowledge and Skills of Quality Management System Auditors

Auditors shall demonstrate the ability to apply a breadth of knowledge and skills which will enable them to be effective in respect of ,

a) Audit principles for both GMP and GDP auditors that ensure audits are conducted in a consistent manner.
   - Seeking agreement with the excipient supplier to audit findings and conclusions
   - Effectively analyzing root cause analysis and resulting corrective/preventative action

b) Knowledge of management system definitions, industry guidance and relevant legislation for auditors of GMP
   - Understanding the application of excipient GMPs to different excipient production processes
     a. Functionality and dosage forms

b. Differing operations to produce the excipient ranging from mineral extraction and purification to chemical or biochemical synthesis

- Applying the excipient GMP audit guide to different situations
- Assessing the adequacy of information systems and technology in support of GMP operations (proper use and control of computer systems (e.g. GAMP 5, EU Annex 11, and 21CFR Part 11)
- An understanding of the following:
  a. Draft IPEC Validation Guide, FDA Guidance on Validation, EU Annex 15
  b. Basic microbiology and chemistry (to be applied to starting materials prior to introduction to excipient manufacture)
  c. Appropriate Pharmacopoeias.
  d. Cleaning principles as applied to manufacturing process
  e. IPEC-PQG Excipient GMPs
  f. Regulations in the intended market.(e.g. TSE, Residual Solvents)
  g. Risk assessment techniques (ICH Q9, HACCP, etc.)
- Regulatory requirements for the excipient in the markets sold

c) Knowledge of management system definitions, industry guidance and relevant legislation for auditors of GDP

- Understanding of different operations of distributors related to distribution and trade of excipients
  a. Operations involving handling of excipients (Note that there may be operations that require GMP as noted in the GDP Annex)
  b. Office-only operations
     - Applying the excipient GDP audit guide to different situations
     - Assessing the adequacy of information systems and technology in support of GDP operations (demonstration of the proper use and control of computer systems)
     - An understanding of distribution related safety and quality systems:
       a. Responsible Care and/or Responsible Distribution Programmes
       b. Distributors assessment systems (e.g. for Europe Safety Quality Assessment Systems European Single Assessment for Chemical Distributors (SQAS ESAD))
     - Regulatory requirements for the excipient in the markets sold

d) Understanding of organisational arrangements and cultures

- General business processes, including those of both the excipient and pharmaceutical industries
- Terminology of both of the excipient and pharmaceutical industries
- Mechanisms used to distribute excipients

7.3.2 Generic Knowledge and Skills of Audit Team Leaders

Audit team leaders shall demonstrate the ability to apply a breadth of additional knowledge and skills in addition to the requirements for generic knowledge and skills for auditors (7.3.1);

Leadership skills can be demonstrated through supervisory experience and leadership experience outside of business, e.g., volunteer organizations.

7.3.3 Specific Knowledge and Skills of Quality Management System Auditors

Auditors shall demonstrate the ability to apply a breadth of knowledge and skills in quality related methods and techniques, knowledge and skills in this area include:

- Use of Quality management tools such as SPC, FMEA, etc.
- Good documentation practices as applied to records
- Demonstration of audit ability e.g. ISO 9001 Registered Lead Auditor, IRCA member, or ASQ Certified Lead Auditor.

7.3.4. Specific Knowledge and Skills of Excipient GMP System Auditors and Audit Team Leaders

a) Specific terminology for the excipient being audited.
b) Excipient GMP quality systems as applied by the manufacturer.
c) Basic understanding of the science and technology of excipient manufacture.
   - Experience working in the excipient industry or with auditing excipient manufacturers

7.4 Education, Work Experience, Auditor Training and Audit Experience

7.4.1 Auditors

7.4.1.1 GMP Auditors shall have

a) Completed an education sufficient to meet the acquisition of the requirements in 7.2 and 7.3

b) Scientific Qualification Work experience
   i. Auditing
   Attended and passed an ISO 9001 or 14000 Certified Lead Auditor course or be an ASQ Certified Quality Auditor or be an IRCA registered Auditor
   ii. Technical, Managerial, and Professional
   - 5 years minimum in the Quality Unit at pharmaceutical ingredient or pharmaceutical company with responsibilities that include conformance to GMP requirements. Suitable alternative experience is 5 years minimum experience performing quality system audit of chemical operations to a recognized standard, e.g. ISO 9001,or
   - GDP Auditors may qualify as GMP auditors if they have 3 years minimum in the Quality Unit at ingredient or pharmaceutical company with responsibilities that include conformance to GMP or GDP requirements. Suitable alternative experience is 3 years minimum experience performing quality system audit of chemical or distributor operations to a recognized standard, e.g. ISO 9001, and 2 years experience as a GDP Auditor

c) Excipient GMP Auditor Training
   - Refer to Appendix A for guidance

d) Excipient Audit Proficiency
   i. Satisfactory assessment from oral examination of the content of the study guide and practical assessment of a simulated audit of an excipient manufacturer or supplier.
   ii. Have successfully completed and supervised one audit to demonstrate:
      - Knowledge of excipient GMP conformance requirements
      - The Certification body should witness and assess their auditors on a periodic basis to ensure that they are maintaining standards. (e.g. Experienced Auditor, one supervised audit within three years to

demonstrating audit skills or other suitable assessment technique approved by Excipact ™.)
- Knowledge of excipient GMP conformance requirements

7.4.1.2 GDP Auditors shall have

a) Completed an education sufficient to meet the acquisition of the requirements in 7.2 and 7.3
b) Scientific Qualification Work experience
   i. Auditing
   Attended and passed an ISO 9001 or 14000 Certified Lead Auditor course or be an ASQ Certified Quality Auditor or be an IRCA registered Auditor
   ii. Technical, Managerial, and Professional
   - 3 years minimum in the Quality Unit at ingredient or pharmaceutical company with responsibilities that include conformance to GMP or GDP requirements. Suitable alternative experience is 3 years minimum experience performing quality system audit of chemical or distributor operations to a recognized standard, e.g. ISO 9001.

c) Excipient GDP Auditor Training
   - 2 days training covering all relevant excipient GDP principles and processes as described in IPEC GDP Guide and related documents plus applicable sections of the IPEC-PQG Excipient Guide.

d) Excipient Auditor Proficiency
   i. Satisfactory assessment from oral examination of the content of the study guide and practical assessment of a simulated audit of an excipient
   ii. Have completed one successfully completed and supervised audit to demonstrate:
   - Audit skills
   - Knowledge of excipient GDP conformance requirements
   - Preparation of audit reports
   - Appropriate rating of findings
   - The Certification body should witness and assess their auditors on a periodic basis to ensure that they are maintaining standards. (e.g. Experienced Auditor, one supervised audits within three years successfully demonstrating audit skills or other suitable assessment technique approved by Excipact ™.)
   - Knowledge of excipient GDP conformance requirements

7.4.2 Audit Team Leaders

- Demonstrated audit knowledge and skills as described in 7.4.1 and confirmed under supervision of a qualified Audit Team Leader and be able to lead & manage an audit team effectively:

7.4.2.1 General

No additional requirements

7.4.3 Auditors who audit both quality and environmental management systems

Not applicable to Excipact ™

7.4.4 Levels of Education, Work Experience, Auditor Training and Audit Experience

a) Auditor for both GMP and GDP

	Auditor	Audit Team Leader
Education 7.4.1.A	Tertiary Scientific Qualification[1]	Tertiary Scientific Qualification
Relevant Audit Experience (7.4.1.Bi)	5 audits prior 2 years	5 GMP audits as Audit Leader prior 2 years
Total Work Experience (7.4.1.Bii)	5 years	5 years general supervisory experience (7.3.2)
Auditor Training in GMP/GDP (knowledge & skills)	7 contact hours	7 contact hours
Auditor training in Excipients	7 contact hours	7 contact hours
Auditor training in the ISO 9001 Quality management (ISO9001:2008 update)	14 contact hours	14 contact hours
Auditor Knowledge Assessment (7.4.1.Di)	Oral or written exam	Oral or written exam
Auditor Assessment (7.4.1.Dii)	1 successful supervised audit	1 successful supervised audit

Note: 1 Examples of such qualifications are Higher National Diploma (UK), Associates Degree (US.).

b) Auditor for GDP only

	Auditor	Audit Team Leader
Education 7.4.1.A	Tertiary Scientific Qualification[1]	Tertiary Scientific Qualification
Relevant Audit Experience (7.4.1.Bi)	5 audits prior 2 years	3 GDP or GMP audits as Audit Leader prior 2 years
Total Work Experience (7.4.1.Bii)	5 years	5 years general supervisory experience (7.3.2)
Auditor Training in GDP (knowledge & skills)	7 contact hours	7 contact hours
Auditor training in the ISO 9001 Quality management (ISO9001:2008 update)	14 contact hours	14 contact hours
Auditor Knowledge Assessment (7.4.1.Di)	Oral or written exam	Oral or written exam
Auditor Assessment (7.4.1.Dii)	1 successful supervised audit	1 successful supervised audit

Note 1 Examples of such qualifications are Higher National Diploma (UK), Associates Degree (US.)

7.5 Maintenance and Improvement of Competence

Auditors and Audit Team Leaders shall achieve this by:

7.5.1 Continual Professional Development

- Attend an annual meeting with programme management to review changes to the programme and programme requirements
- Attend organizational meetings relevant to excipient GMP
- Attend organisational meetings relevant to excipient manufacturing and distribution technology and processes

7.5.2 Maintenance of Auditing Ability

- Minimum of 1 audit per year of excipient GMP or GDP audit.
    - Return to the requirement for 1 successful supervised audit.

7.6 Auditor Evaluation

Auditors and Audit Team Leaders shall have on at least a biannual basis (i.e. minimum every 2 years):

7.6.1 General

- A documented evaluation that they continue to have required skills, comprising
    - A review of audit reports
        - As audit Team Leader
    - An observation of audit skills
        - As reported for Auditors by Audit Team Leader
        - As reported by a management representative who witnessed an audit to observe the Audit Team Leader

7.6.2 Evaluation Process

- An annual records Review
    - Analysis of new records of further education, training, employment and excipient GMP audit experience since the last review
- Feedback
    - Surveys, questionnaires, complaints, etc. from applicants and others
    - Audit Team Leader feedback on team participants
- Interview
    - Face to face interview
- Observation
    - Witnessed audits *for Audit team leader Every 3 years*
- Maintenance of credentials
    - Certifications achieved, e.g. ASQ CQA, IRCA Registered Lead Auditor, or ISO 9001 Certified or Registered Lead Auditor
- Post Audit Review
    - Review of the audit reports and discussion with audit participants

The continued acceptance or non-acceptance of the Audit Team Leader or Auditor shall be recorded after these assessments.

Section 1 GENERAL

1.1 Auditor Roles

In order to manage the complexities of excipient audits and the roles of team members involved, two auditor roles have been established.

- Auditor (including experienced GMP/GDP auditor)
- Audit team leader

These two roles are differentiated by the extent of the responsibilities assigned to each grade and the potential line management responsibilities that are commensurate with the Audit Team leader grade.
Auditors and Audit team leaders will require shared initial foundation experience and knowledge, whereas the audit team leader will require additional skills in areas such as experience in excipient auditing and team management skills.

1.2 Attaining role status

In order to achieve the role of auditor or audit team leader it is necessary to demonstrate generic evidence.

1.3 Qualifications and Experience

The attributes detailed within the Study Guide (section 2) are considered as they set a minimum knowledge and experience requirement without which the auditor or audit team leader is unsuitable. The study guide is designed to clearly highlight the expected skills for each grade of auditor.
Professional experience and work based experience is an important element in assessing the suitability of candidates for the position of auditor and audit team leader.
Experience can be demonstrated through a combination of specific audit training evidence and practical application of the original training.
There is a particular requirement to gain expertise in excipient auditing which can be achieved as stated below.
In certain situations there may be more than one way in which an applicant may be successful.

Section 2 STUDY GUIDE - PROFESSIONAL/WORK BASED EXPERIENCE and TRAINING

Education (7.4.1.a)
Education requirements for Auditor and Audit Team Leader

- Tertiary Scientific Qualification - Examples of such qualifications are Higher National Diploma (UK), Associates Degree (US).

Relevant Audit Experience (7.4.1.bi)
Experience requirements are defined below. The applicant should be able to demonstrate/show evidence of the content and scope of the audits performed and the applicant's involvement in the audits:

- Auditor - 5 audits prior 2 years. These audits must in relation to ISO 9001 and/or ISO 14001.
- Experienced GMP/GDP auditor - 5 GMP audits prior 2 years. These audits must be in relation to FDA and EU GMPs.
- Audit Team Leader - 5 GMP audits as Audit Leader prior 2 years.

Quality Management
This is applicable to both auditors and audit team leaders
Candidate auditors should be able to demonstrate:-

- The knowledge and skills, as defined in 7.3.1 and 7.3.3, to include:-

- Audit principles
- Knowledge of management system definitions, industry guidance and relevant legislation - Management System and Reference Documents
- Understanding of organizational arrangements and cultures
- Knowledge and skills to understand the regulatory context with respect to: Processes and Products, including services

This may be achieved primarily through experience as a GMP auditor or ISO 9001, ISO 14001 Registered Lead Auditor.

Candidate Audit Team Leaders auditors should be able to demonstrate:-

- The additional knowledge and skills as defined in 7.3.2.
- Adequate experience in excipient GMP and GDP auditing

GMP

Candidate auditors should be able to demonstrate the following knowledge and skills:-

- GMP knowledge and Skills
  - Knowledge of the GMP excipient guides, primarily the IPEC/PQG guide and other relevant guidelines
  - Capable of evaluating the interaction between various departments to assure conformance
  - Capable of assessing the adequacy of information systems and technology in support of GMP operations (proper use and control of computer systems i.e. GAMP, EU Annex 11, and 21CFR Part 11)
  - An understanding (demonstrated by education, experience, or qualifications) in the following areas:
    - Draft IPEC Validation Guide, FDA Guidance on Validation, EU Annex 15
    - QMS Risk assessment techniques (ICH Q9, HACCP, etc.)
    - Employee Training in GMP principles as appropriate for their position
  - Processes and Products, including services: Knowledge and skills to understand the regulatory context
    a) Excipient and pharmaceutical industry terminology
    b) Impact of Technical characteristics of processes on products,
    c) Services typically provided

GDP

Candidate auditors should be able to demonstrate knowledge of the entire content of the IPEC GDP Guide for Pharmaceutical Excipients.

Excipients

Candidate auditors should be able to demonstrate the following knowledge and skills:-

- Excipient specific knowledge and skills
  - Understanding the application of excipient GMPs to different excipient production processes, with respect to:-
    - Functionality and dosage forms of the end use
    - Differing operations to produce the excipient ranging from mineral extraction and purification to chemical or biochemical synthesis (for example).
  - Basic microbiology

- as applicable to starting materials prior to introduction to excipient manufacture and throughout the manufacturing process
- with respect to microbiological quality of water use within the process

- Basic chemistry, as applicable to starting materials prior to introduction to excipient manufacture and throughout the manufacturing process
- Appropriate Pharmacopoeias.
- Cleaning principles as applied to manufacturing process
- IPEC-PQG Excipient GMPs and GDPs and references as appropriate
- Regulations in the intended market.(i.e., TSE, Residual Solvents)
- Organizational Situations:
  - Distribution of excipients and appropriate regulations
  - Business processes of both excipient and pharmaceutical industries
  - GMP requirements for the excipient in the markets sold
- Processes and Products, including services: Knowledge and skills to understand the regulatory context
  - Technical characteristics of the processes and products being audited, including services typically provided
  - Specific terminology for the excipient being audited.
  - Excipient GMP quality systems as applied by the manufacturer.
  - Basic understanding of the science and technology of excipient manufacture:
    - Experience working in the excipient industry or with auditing excipient manufacturers
    - Continuing education appropriate to the excipient

Personal Attributes (7.2)

Attributes desired are:

a) Ethical-Must acknowledge the potential for bias or conflict of interest

b) Open minded-Excipient industry is quite diverse in their operations

c) Diplomatic
   - Avoid being drawn into the role of consultant in the discussion of audit findings with the auditee.

d) Observant-Particular emphasis on the possibility for contamination of the excipient

   "All auditors need to be able to gather audit evidence. In excipient GMP auditing much evidence can be gathered using the senses. It requires an inquisitive stance and the desire to find out what is actually happening. Auditors will also need to be able to engage in a wide range of topics and ask all manner of questions. It is important to stay focused and not to become side-tracked by areas that are not directly relevant to the audit." **Note: from IRCA Knowledge Bank**
   - Have the instinct to associate observations with the overall perception of the site leading to objective evaluation and further investigation.

e) Perceptive

   "be able to work out an understanding of the cause and effect linkages within the auditee's management system" **Note: from IRCA Knowledge Bank Identify hazards that may put the excipient at risk**

f) Versatile-Ability to interpret the standard to the situation e.g. no smoking also would preclude no chewing of tobacco

g) Tenacious-Maintain integrity to the audit and the standard with critical points e.g. no eating or smoking where inappropriate

h) Decisive
i) Self-reliant
j) Personal Development-Be supportive of the need for continuing development

Total Work Experience
See 7.4.1.bii and 7.4.4

Auditor training in GMP/GDP (knowledge and skills)
The applicant must be able to demonstrate 7 contact hours training in core knowledge points, to include but not limited to:-

- Equipment qualification and validation (scientific techniques used to demonstrate a state of control e.g. validation, SPC, DOE)
- Pharmacopeia and laboratory requirements for QC testing.
- Cleaning principles as applied to manufacturing process
- ½ hour education on "Where excipient GMP begins"
  - ½ hour training on assessment or review of risk based on route of administration
- 1 hour audit report writing and rating findings

Auditor training in excipients (7.4.1.1.c)
The applicant must be able to demonstrate 7 contact hours training in excipient GMP conformance requirements, to include but not limited to:-

- Contamination control - particular attention must be paid where the excipient can become contaminated.
- Review of starting point for excipient GMP
  - Review of additional GMP expectations for Assessment or review of risk based on route of administration
- 1 hour overview of the Excipient GMP certification program
  - Include conflict of interest
  - Confidentiality

Auditor training in GDP (knowledge and skills) (7.4.1.2.c)
The applicant must be able to demonstrate 7 contact hours training in core knowledge points as included in the IPEC GDP Guide for Pharmaceutical Excipients:

- Quality Management
- Organization and Personnel
- Premises
- Warehousing and Storage
- Equipment
- Documentation
- Repackaging and Relabelling
- Complaints
- Recalls
- Returned goods
- Handling of non-conforming materials
- Dispatch and Transport
- Contract activities

Auditor training in the ISO 9001 Quality management (ISO9001:2008 update)
14 Contact hours

To be added collectively and later

Foreword to this Annex

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

a) Conforms to specified requirements,
b) Is capable of consistently achieving its stated policy and objectives,
c) Is effectively implemented, and
d) Regularly assessed.

This part of Excipact ™ provides generic requirements for certification bodies performing audit and certification in the field of an excipient GMP quality management system. Such bodies are referred to as Certification Bodies. Certification activities involve the audit of an organization's quality management system.

This document is an annex to ISO/IEC 17021, Conformity assessment requirements for bodies providing certification of excipient management systems, as this is the most appropriate publicly available document commonly used by 3rd party audit organisations. The headings and sections in this document are those of ISO/IEC 17021 and any additional text stipulates requirements to be implemented together with the ISO/IEC 17021 clauses in order to perform Excipact ™ GMP and GDP certification assessments.

Where a heading or section of ISO/IEC 17021 is omitted then there are no additional requirements to those already stipulated in ISO 1702.

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

The main text that follows is based on the headings in ISO/IEC 17021:2006 and the details are the Excipact ™ requirements:

Text in Bold are ISO/IEC 17021 Headings

Standard Text are Excipact ™ requirements.

Italicised text is from ISO/IEC 17021:2006

EXCIPACT ™

Conformity assessment-Requirements for bodies providing certification of excipient management systems

1. Scope

The standard contains the principles and requirements for the management system operated by Excipact ™ certification bodies. The requirements assure the impartiality, competence and consistency of Excipact ™ audits and the certification of the quality management systems of Excipient suppliers.

2. Normative References

ISO/IEC 17021: Conformity assessment – Requirements for bodies providing audit and certification of management systems

3. Terms and definitions

Certified auditee: Organization whose quality management system has been certified to Excipact ™.

Auditee: The excipient supplier being assessed.

Debarred: A person who is restricted by a governmental authority from working for or contracting to a drug product manufacture in any capacity

GMP GMP is that part of quality assurance which ensures that products are consistently produced and controlled to the quality standard appropriate to their intended use in the pharmaceutical industry and as required by the product specification. The terms “current Good Manufacturing Practices” (cGMP) and “Good Manufacturing Practices” are equivalent.

GDP GDP is that part of quality assurance which ensures that products are consistently handled and controlled during the supply chain from the original manufacturer to the final user according to the quality standards appropriate to their intended use in the pharmaceutical industry and as required by the product specification and other regulatory requirements.

4. Principles

4.1 Principles that inspire confidence include:

No additional requirements

4.2 Impartiality

It is essential that 3rd party audit organizations base decisions on objective evidence collected at audit, from which they can judge conformity or non-conformity to the Excipact ™ GMP and/or GDP requirements. Such decisions shall not be influenced by other interests or other parties.

4.3 Competence

The requirements for auditor competency set out in the Excipact ™ Section dealing with the requirements for auditor competency shall be met.

4.4 Responsibility

The auditee has the responsibility for conformance to the ISO 9001 and Excipact ™ GMP or GDP certification requirements.

The certification body has responsibility to assess the auditee against ISO 9001 and Excipact ™ GMP and/or GDP requirements.

4.5 Openness

No additional requirements

4.6 Confidentiality

Non-public information gathered as part of the audit process shall not be disclosed to other parties without the permission of the auditee

4.7 Responsiveness to complaints

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. The 3rd party audit organization shall make publically available a statement that indicates it understands the criticality of impartiality in carrying out GMP and / or GDP certification assessments, that it manages conflicts of interest and ensures the objectivity of its certification activities.

5.2.2. The 3rd party audit organization shall have a documented risk assessment that evaluates threats that could result in conflicts of interests arising from certification activities and the attendant relationships. No individual shall be involved in the certification process if they provide consultation on excipient GMP conformance to the auditee (see 5.2.5).

5.2.3. No additional requirements.

5.2.4. No additional requirements

5.2.5. The certification body or any auditor (including ex-employees or consultants) shall not provide management system, GMP or GDP consulting within two years of the completion of any certification of the auditee.

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. No additional requirements.

5.2.11. No additional requirements.

5.2.12. No additional requirements.

5.2.13. All personnel associated with certification shall be required to notify top management of the certification body of any threats or potential threats to impartiality.

5.3. Liability and financing

No additional requirements

6. Structural requirements

6.1. Organizational structure and top management

6.1.1. No additional requirements.

6.1.2. The certification body shall identify the top management (board, group or persons, or person) having overall authority and responsibility for the following:

j) Oversight of the appeals process.

6.1.3. No additional requirements.

6.2. Committee for safeguarding impartiality

6.2.1. No additional requirements:

6.2.2. If top management does not respect the advice of the committee, the committee shall have the authority to inform Excipact ™.

6.2.3. No additional requirements.

7. Resource Requirements

7.1. Competence of management and personnel

7.1.1. The certification body shall have processes to ensure that personnel have appropriate knowledge in GMP and / or GDP management systems. The competence requirements shall be established and annually demonstrated to Excipact ™ in accordance with the auditor competency section of Excipact ™ (see also 7.2.10).

7.1.2. No additional requirements.

7.1.3. The certification body shall have access to the necessary technical expertise on excipient regulations, GMP and / or GDP within the geographic areas 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. The certification body shall designate a qualified auditor to act as supervisor in the qualification of auditors. The supervisor shall be a Lead Auditor in the program and display appropriate skills to supervise candidate auditors.

7.2.5. The certification body shall demonstrate effective auditing in conformance to the Excipact ™ auditor competency requirements.

7.2.6. No additional requirements.

7.2.7. Auditors and technical experts shall only be used for certification activities where they have demonstrated competence as stipulated in Excipact ™ Auditor Competency Requirements.

7.2.8. The certification body shall identify ongoing training needs and provide access to training for all personnel in accordance with Excipact ™ Auditor Competency Requirements.

7.2.9. Those individuals, who are 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. The technical experts shall be independent and free from conflict of interest of the audit process they are to review. The technical experts shall have proven knowledge and experience in the pharmaceutical and/or excipient industry.

7.2.10. There shall be annual performance evaluation of those involved in the certification programme plus assessment of audit skills every 3 years. Competence evaluations shall lead to identification of training needs.

7.2.11. Monitoring of auditor performance includes a combination of on-site observation, review of audit reports and feedback from auditees or the market (regulators, pharmaceutical makers) in accordance with ISO 19011 Section 7.4.1d) and the corresponding section in the Excipact ™ Auditor Competency Requirements.

7.2.12. There shall be periodic on-site observation of auditor performance not to exceed 3 years in accordance with Excipact ™ Auditor Competency Requirements.

7.3. Use of individual external auditors and external technical experts

No additional requirements.

7.4. Personnel records

No additional requirements

7.5. Outsourcing

The certification body shall not delegate responsibility for certification to another organization. Where it requires additional resources to perform certification activities those resources shall satisfy the requirements in this standard (see 7.2, 7.3, 7.4).

The certification body shall have documented procedures for qualification and monitoring of outsourced services.

8. Information requirements

8.1. Publicly accessible information

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

8.1.2. No additional requirements

8.1.3. Certifications granted, suspended, or withdrawn must be reported to Excipact ™ who will make such information publicly available.

8.1.4. The certification organization shall provide the means to validate a given certification, and the associated audit reports.

8.2. Certification Documents

No additional requirements

8.3. Directory of certified auditees

Excipact ™ shall maintain a directory of valid certifications, including the name, standard, scope and geographical location, for each certified auditee.

8.4. Reference to certification and use of marks

8.4.1. Excipact ™ requirements for the certification policy include:

1) Excipact ™ will issue a unique number for each certificate issued by the certification body. This number is to be used as a component of the Certified Excipient Mark.
2) Certified Organizations are entitled to use the Certified Excipient Mark on letter headings, business cards, brochures, advertisements and other promotional material including vehicles. The Mark may also be used on outer packaging, trade samples and flags.
3) The Certified Excipient Mark may be reproduced in any size but should not be displayed where the resulting printed definition becomes unclear or the text (including a unique number whose prefix identifies the certification body that granted certification) becomes unreadable to the naked eye.
4) The Mark must be reproduced in its entirety, including the surrounding outline.
5) The Mark may be reproduced in any colour.
6) The Certified Excipient Mark must not be used on, or closely associated with, products in such a way as to imply that the product itself is certified.
7) The company is required by contract to use the mark as required by Excipact ™.

8.4.2. The mark may only be applied to the Certificate of Analysis where the mark is displayed as part of the document letterhead and does not convey the impression that certification includes verification of excipient quality.

8.4.3. The certification body shall require that the auditee organization:

f) Does not allow reference to certification to imply certification of the excipient

8.4.4. The certification body exercises control of ownership and takes action to deal with incorrect references to certification status or misleading use of certification documents, marks, or audit reports. The certification body shall notify the excipient certification programme owner of any such incidents.

8.5. Confidentiality

No additional requirements

8.6. Information exchange between a certification body and its auditees

8.6.1. Information on the certification activity and requirements

No additional requirements

8.6.2. Notice of changes by a certification body

Upon receipt of changes from Excipact ™, an implementation plan shall be developed by the certification body which comprises the following:

i. Description of the change to the Certification Programme,
ii. Potential impact of the change to the auditees,
iii. Timeframe within which the applicants are to implement the change,
iv. Verification schedule that the change by applicants has been completed

There shall be

- A prompt verification of programme changes
- A review of confirmatory documentation, or
- On-site verification at the next scheduled site audit that changes have been implemented
- Establishment of a future effective date by which all applicants must comply with the new requirements, otherwise their right to issue Excipact ™ certificates is suspended.

8.6.3. **Notice of changes by an auditee**

No additional requirements.

9. Process Requirements

9.1. General Requirements

9.1.1. There shall be a two-stage initial audit. At least annually, aspects of the GMP and / or GDP Annex will be assessed. Every third year there shall be a complete audit report covering the GMP and / or GDP Annex for review by the technical experts who recommend recertification. Audits shall be adjusted according to the scope and complexity of the GMP / GDP system and excipients produced.

9.1.2. No additional requirements.

9.1.3. Additional requirements.

- Where the audit is conducted to certify conformance with ISO 9001 plus the GMP/GDP Annex, the audit team shall include an ISO 9001 Registered Lead Auditor.
- Where the audit is conducted solely to the GMP/GDP Annex, the audit team does not require an ISO 9001 Registered Lead Auditor.

9.1.4. The time allotted for the audit shall be adequate to assess conformance to excipient GMP / GDP requirements in addition to any time required for any concurrent ISO 9001 assessment. In determining the time required the following shall be considered,

i. The number of excipients manufactured at a location, and the differences in chemistry used to prepare them
ii. The complexity of the technology and the management systems used to manufacture the excipients
iii. Any other activities within the scope of the certification
iv. The number of sites on which the activities occur that are within the scope of the audit.

The following is provided as a guide only for planning adequate time to assess the site:

Complexity	Initial assessment (auditor days)		Annual surveillance visits (auditor days)	
Assessment scenario	Total	On-site	Total	On-site
1. Single Excipient / Simple arrangements	5	4	2.5	2
2. Multiple grades <> chemistry	6.5	5	1.5	1
3. Multiple grades, <> equipment	6.5	5	2	1.5
4. Multiple excipients	7.5	6	3.75	3
Additional Time for:				
1. Off-site operations	0.25-0.5	0.25-0.5	0.25-0.5	0.25-0.5[1]
2. Complex operations	0.25-0.5	≥0.25	0.25-0.5	≥0.25

9.1.5. The certification body shall audit all sites that product the excipient at initial certification. Once evidence is in place to demonstrate the quality Management systems at each of the sites are the same, then further surveillance and re-assessment audits can be performed on a risk based frequency. This risk assessment shall consider the known use and application of the products made at those sites with higher frequencies required where the excipient use poses higher potential risks to patients.

9.1.6. No additional requirements:

9.1.7. No additional requirements.

9.1.8. No additional requirements.

9.1.9. No additional requirements.

9.1.10. The audit report shall contain sufficient information and detail to allow the certification board to accurately assess the compliance of the auditee against the Excipact ™ GMP and or GDP requirements and include:

- Name of the company,
- Location of the site audited,
- Dates of the site audit,
- Names and qualifications of audit team members,
- Scope of operational activities covered by the audit,
- Name of the excipient(s) audited including both monograph and trade names, and
    i. Objective evidence for each section audited,
    ii. Reference to the clause for each observation above
- Rating for each observation: acceptable, critical, major, or minor.

9.1.11. The auditee shall be required to provide root cause analysis and corrective measures within a proscribed timeframe.

- Applicants shall be given an opportunity to correct findings and the draft audit report for errors or omissions.

[1] Surveillance audit may be conducted only once during the recertification interval.

- Implementation of appropriate preventive or corrective measures shall be confirmed.
  i. If a finding can be remedied while the audit is progressing, the corrective measure shall be noted in the audit report.
  ii. If a finding can be remedied prior to the decision on certification the audit report shall reflect the remediation so that consideration can be given to the decision on certification.
  iii. If certification is granted contingent upon the implementation of stated corrective or preventive measures, completion by their due date shall be verified by the Certification Body through appropriate means, e.g. document review, site visit, etc. and the audit report shall be updated.
- The auditee shall be encouraged to submit a corrective action plan. The plan, if provided, shall be included with the audit report for review under 10.2.5.1.

9.1.12. The certification body shall ensure at least one auditor (ideally the audit team leader) who performed the assessment of the auditee has determined the adequacy of corrective measures.

9.1.13. No additional requirements .

9.1.14. No additional requirements.

9.1.15. The certification body shall confirm, prior to making a decision, that:
a) The audit report contains sufficient information
b) The corrective measures have been reviewed, accepted, and verified for effectiveness for all nonconformities that represent:
  i. Failure to fulfil one or more requirements of GMP / GDP, or
  ii. Raise significant doubt about conformance of the quality system to GMP / GDP.

9.1.16 The certification body shall provide a service to auditees which permits audit reports to be authenticated (auditees may issue audit reports to their customers)..

9.2. Initial Audit and Certification

9.2.1. Application
No additional requirements

9.2.2. Application review

9.2.2.1. Before proceeding with the audit , the certification body shall conduct a review of the application and supplementary information for certification to ensure that:
g) the certification is for excipient GMP and or Excipient GDP,
h) safety issues have been identified

9.2.2.2. No additional requirements.

9.2.2.3. No additional requirements.

9.2.2.4. No additional requirements.

9.2.3. Initial certification audit

9.2.3.1. Stage 1 audit

9.2.3.1.1. The Stage 1 audit is performed to assess the auditee's QMS and discuss preparation for the Stage 2 audit

Note: The Stage 1 audit can be used to determine the duration of the Stage 2 audit.

9.2.3.1.2. No additional requirements

9.2.3.1.3. No additional requirements.

9.2.3.2. **Stage 2 audit**

The Stage 2 audit is to evaluate implementation and effectiveness of the management system and includes:

a) Information and evidence of conformity to excipient GMPs / GDPs
b) Links between normative requirements, policy, performance objectives, and targets consistent with the expectations of excipient GMPs / GDPs, any regulatory requirements, responsibilities, competence of personnel, operations, procedures, performance data, and internal audit findings and conclusions.

9.2.4. **Initial certification audit conclusions**

No additional requirements.

9.2.5. **Information for granting initial certification**

Non-conformances or findings shall be classified as critical, major, or minor

Critical: The excipient poses an immediate risk to patient safety. Remediation before further excipient is produced would be indicated and/or a recall should be considered.

Major: Evidence indicates that the Quality Management System is not effectively developed or implemented. For instance, the system is poorly designed or not followed; or multiple or repetitive minor nonconformities in the same aspect of the quality management system..

Minor: A departure from the standard that is neither a critical nor major. Action to rectify the finding is indicated.

For Certification the acceptance criteria are:

1. No items rated as Critical.
2. No items rated as Major.

For continuing Certification, the Surveillance audit shall have:

1. No items rated as Critical.
2. No items rated as Major unless the deficiency has been remediated or an interim control is in-place i.e. CAPA plan accepted by the Certification Body and verified.
3. No items rated as Minor from a prior audit that have either not been corrected or for which an acceptable CAPA plan has not been developed.

9.2.5.1. No additional requirements .

9.2.5.2. No additional requirements.

9.2.6. **Issuing certification and audit reports**

9.2.6.1 Following a positive assessment, the certification body shall provide the auditee with an Excipact ™ Certificate. This shall contain the following as a minimum:

- The name of the auditee
- The address of each approved location
- The initial date of certification
- The date of the latest recertification

- A statement indicating if certification has been continually held between the initial data and the latest certification date
- The date of recertification
- The scope of the assessment at each assessed location, including details of the product ranges manufactured or distributed at those locations.

9.2.6.2 The certification body shall provide a means of authenticating Excipact ™ certificates to 3rd parties who may require confirmation of their validity.

9.2.6.3 The certification body shall provide an audit report to the auditee for each assessment, reassessment and surveillance audit.

9.2.6.4 The certification body shall provide an audit report to the auditee which has been edited at the auditees request to redact confidential information. This information shall only be redacted if it has no impact on the assessment outcomes (e.g. removal of non-conformities or other assessment outcomes). The auditee shall be given permission to allow it to share audit reports so long as the whole report is issued..

Note: The purpose of the redacted version of the audit report is to allow the auditee to issue it to their customers as additional assurance of the capability of their quality management system.

9.2.6.5 The certification body shall provide an authentication service to those excipient users who require confirmation that the audit report has been prepared by the certification body, and is unaltered from the one originally issued.

9.3. Surveillance activities

9.3.1. General

9.3.1.1. No additional requirements.

9.3.1.2. No additional requirements

9.3.2. Surveillance audit

9.3.2.1. No additional requirements:

9.3.2.2. Surveillance audits are conducted at least annually plus half of the quality system such that the entire excipient quality system has been reviewed by the two surveillance audits.

9.3.3. Maintaining certification

No additional requirements

9.4. Recertification

No additional requirements

9.4.1. Recertification audit planning

9.4.1.1. Recertification shall occur at intervals of not more than 3 years after initial certification or last recertification. The recertification audit shall be planned and conducted to confirm the requirements of excipient GMP /GDP continue to be met.

9.4.1.2. No additional requirements.

9.4.1.3. No additional requirements.

9.4.1.4. The audit should assess all sites covered by the certification and be conducted triennially.

9.4.2. **Recertification audit**

9.4.2.1. No additional requirements:

9.4.2.2. No additional requirements.

9.4.3. **Information for granting recertification**

No additional requirements

9.5. Special audits

9.5.1. **Extensions to scope**

No additional requirements

9.5.2. **Short-notice audits**

No additional requirements

9.6. Suspending, withdrawing or reducing the scope of certification

9.6.1. No additional requirements

9.6.2. The certification body shall suspend certification in cases when, for example:

- There have been persistent or serious failures to meet certification requirements
- A regulatory authority inspection has found significant deviation from GMP / GDP requirements that meets the definition of critical finding (see 9.2.5),
- The auditee has not paid his certification fee within the prescribed period

9.6.3. Under suspension, the auditee shall refrain from promoting its certification. The certification body shall notify Excipact ™ of the auditee suspension.

9.6.4. No additional requirements.

9.6.5. No additional requirements.

9.6.6. No additional requirements

9.6.7. 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. No additional requirements.

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

d) Where the appeal cannot be resolved to the satisfaction of the auditee, the appeal shall be escalated to Excipact ™.

9.7.6. No additional requirements.

9.7.7. No additional requirements.

9.7.8. Formal notice is to be given to the petitioner at the closure of the appeal by the Certification Body. If not satisfied, the petitioner can appeal to Excipact ™ whose decision is final.

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. No additional requirements.

9.8.7. No additional requirements

9.8.8. No additional requirements.

9.8.9. No additional requirements t.

9.8.10. The Certification body, together with the auditee and complainant, shall determine the extent to which the complaint and resolution is made public. If not satisfied with the complaint resolution process or decision, the auditee or complainant can raise the matter with Excipact ™ whose decision is final.

9.9. Records of applicants and auditees

9.9.1. No additional requirements.

9.9.2. No additional requirements:

9.9.3. No additional requirements.

9.9.4. No additional requirements.

10. Management system requirements for certification bodies

10.1. Options

The certification body shall have a management system that meets the requirements of clauses 5-9 and ISO Guide 65, ISO Guide 17021 or equivalent.

10.2. Option 1: Management system requirements in accordance with ISO 9001

No additional requirements

10.3. Option 2: General management system requirements

10.3.1. **General**
No additional requirements

10.3.2. **Management system manual**
No additional requirements.

10.3.3. **Control of documents**

10.3.4. No additional requirements

10.3.5. **Control of records**
No additional requirements.

10.3.6. **Management review**

No additional requirements

10.3.7. **Internal audits**
10.3.7.1. No additional requirements.

10.3.7.2. Audits shall be planned using a risk-based approach to areas covered.

10.3.7.3. No additional requirements.

10.3.7.4. No additional requirements:

10.3.8. **Corrective actions**
No additional requirements

10.3.9. **Preventive actions**
No additional requirements:

These will be added at a later version

