IPEC FEDERATION

Pharmaceutical Quality Group

The International Pharmaceutical Excipients Council

& The Pharmaceutical Quality Group

The Joint Good Manufacturing Practices Guide

For Pharmaceutical Excipients

This document represents voluntary guidance for the excipient industry and the contents should not be interpreted as regulatory requirements. Alternatives to the approaches in this Guide may be used to achieve an equivalent level of assurance for excipient quality.

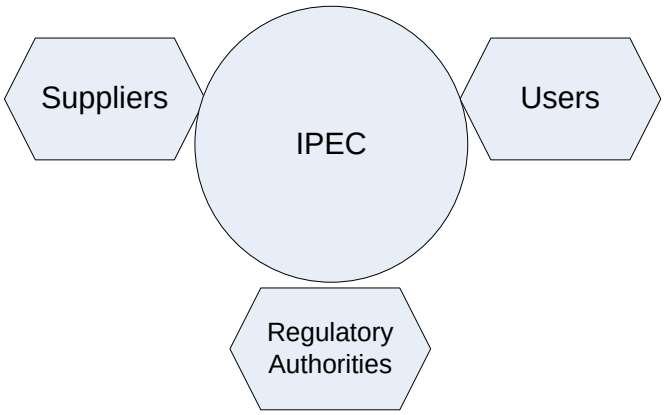
FOREWORD

IPEC

The IPEC Federation is a global organization that promotes quality in pharmaceutical excipients and represents the five existing regional International Pharmaceutical Excipient Councils - IPEC-Americas, IPEC China, IPEC Europe, IPEC Japan, and IPEC India - and provides a unified voice to promote the best use of excipients in medicines as a means of improving patient treatment and safety.

IPEC has three major stakeholder groups:

1. Excipient manufacturers and distributors, who are considered suppliers in this document.
2. Pharmaceutical manufacturers, who are called users.
3. Regulatory authorities who regulate medicines.



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, see www.pqg.org

This document offers best practice and guidance on the content of an excipient **Good Manufacturing Practices Guide.** It is important that the reader confirms this is the latest version of the guide as found on the appropriate website at ipec.org or pqg.org

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ACKNOWLEDGEMENTS

This Guide was developed by representatives of the members companies of The International Pharmaceutical Excipients Council Federation (IPEC) and the Pharmaceutical Quality Group (PQG).

IPEC and PQG greatly appreciate the many hours devoted by the core team of individuals and other contributors listed below, to make this Guide available to IPEC members and the broader excipient community. Equally, IPEC and PQG extend their thanks to the employers of those same contributors who provide the necessary time and resources, without which, this Guide would not be possible.

CORE REVISION TEAM

IPEC

Lars Albermann, Merck
Wiebke Baehker, Merck
Marta Cabrera, Croda
Frederik De Vos, Janssen Pharmaceutica
Rainer Fendt, BASF
Albin Lannoy, Roquette Freres
Roberto Mastrantonio, Eli Lilly
Kevin McGlue, Colorcon
Andreas Pfrengle, Grace
Astrid Stockrahm-Uhling, DFE Pharma
Beverley Stout, GlaxoSmithKline

PQG

Ian McKeown, PQ Silicas
Stephen Moss, GlaxoSmithKline

JOINT IPEC – PQG GOOD MANUFACTURING PRACTICE GUIDE FOR EXCIPIENTS 2017

1 INTRODUCTION

1.1 Purpose and Scope

The quality of excipients is critical to assure the safety, quality and efficacy of medicines. Excipients have a wide range of applications and are essential components of the drug product formulation. Characteristics that excipients impart to formulated drug products include cosmetic appearance, stability and delivery of the active ingredient. Therefore, applying appropriate Good Manufacturing Practice (GMP) principles to excipients is essential. There are a large number of applications for this diverse range of materials which makes the development of excipient GMP guidelines challenging.

Increasingly users of excipients are required by regulatory authorities to assure patient safety through the evaluation of risks and application of suitable GMP to the manufacture and supply of each excipient. This document proposes GMP appropriate for the manufacture of excipients and is a joint initiative between the International Pharmaceutical Excipients Council (IPEC), and the Pharmaceutical Quality Group (PQG). It was first published in 2006 incorporating the IPEC Good Manufacturing Practices Guide for Bulk Pharmaceutical Excipients 2001 with the PQG's PS 9100:2002 Pharmaceutical Excipients.

This document is applicable to the manufacture of excipients intended for use in drug products. It covers the quality management system and the extent of GMP necessary throughout manufacturing for both batch and continuous processes. Reference is made to other publications and standards, such as the EXCiPACT GMP and GDP or NSF/IPEC/ANSI-363 2014 standards.

The manufacture of certain excipients for specialist applications presents additional challenges that are outside of the scope of this Guide. Examples include excipients;

- for parenteral, ocular, inhalation, open wound use,
- that are sterile and/or pyrogen free.

In these cases, it is recommended that guidelines and compliance programmes that provide detailed guidance for the manufacture of the related drug products be consulted and adapted as necessary to the excipient in question.

For additional guidance relating to Good Distribution Practices (GDP) refer to the IPEC Good Distribution Practices Guide.

1.2 Principles Adopted

1.2.1 The Guide and its Use

Excipients are diverse and often have uses other than for pharmaceutical applications. Each manufacturer should consider how this Guide might apply to their products and processes (for example batch *versus* continuous processes). Since excipients are so diverse, some principles of this Guide may not be applicable to certain products and manufacturing processes.

For the purposes of this Guide the terms GMP and current Good Manufacturing Practice (cGMP) are equivalent.

The term "should" indicates recommendations that are expected to apply unless shown to be inapplicable or replaced by an alternative that provides at least an equivalent level of quality assurance. Note that "should" does not mean "must" or "shall".

1.2.2 Application

The text provides the guidance necessary for the manufacture of excipients, but not all of the details. As an international guidance document, it cannot specify national legal requirements or cover particular characteristics of every excipient.

1.2.3 Quality System Standard

The quality management system standard chosen as a framework for this Guide is ISO 9001, which is appropriate for manufacturing facilities. A manufacturer may apply the ISO standard with or without certification, but this is a business decision and not a recommendation of this Guide. However, ISO certification has the benefit of providing assurance to customers that the excipient manufacturer's quality management system has been independently verified.

IPEC and the PQG believe that merging GMP principles for excipient manufacturing into the ISO 9001 quality management system enhances not only quality management but also an organization's operational procedures. The organization may also seek certification to an excipient GMP standard such as EXCiPACT.

1.3 Layout

The headings in this document have been aligned with the ISO 9001:2008 clause numbers, because many excipient manufacturers already use the ISO 9001 standard as a basis for their quality management system. Additional headings are included as required to introduce the additional guidance on GMP when not covered by ISO 9001 clauses. A further revision of this Guide to ISO 9001:2015 clause structure is in preparation.

Section 3 General Guidance provides an overview of the GMP criteria applicable to excipient manufacture and the point of application of excipient GMP.

Sections 4 to 8 give guidance on the GMP principles and implementation of a quality management system suitable for excipient manufacture. No attempt has been made to include details specific to particular excipients. Individual manufacturers should address these as they apply to their own products and processes.

Appendix A covers excipient GMP Auditing Considerations, which describe key criteria to be considered when auditing an excipient manufacturing facility.

2 DEFINITIONS

Refer to the *International Pharmaceutical Excipient Council Glossary: General Glossary of Terms and Acronyms.*

3 GENERAL GUIDANCE

International regulations governing drug products require that they be produced, processed, packed and stored in accordance with GMP. Unlike pharmaceutical products and APIs, there was previously little guidance specifically addressing excipients manufacture.

3.1 Excipients

Excipients are substances other than the API, which have been appropriately evaluated for safety and are intentionally included in a drug delivery system.

For example, excipients can:

- aid in the processing of the drug delivery system during its manufacture,
- protect, support or enhance stability, bioavailability or patient acceptability,
- assist in product identification,
- enhance any other attribute of the overall safety, effectiveness or delivery of the drug product during storage or use.

3.2 Excipient GMP Implementation

The application of GMP is relevant once it has been determined that a chemical is intended for use as a component of a drug product. Excipient manufacture should be carried out in accordance with the GMP concepts consistent with this Guide. The objective of excipient GMP is to ensure that the manufacture of an excipient results in a consistent material with the desired quality characteristics. The emphasis of GMP for excipients is to assure product integrity, avoid product contamination and ensure that records are maintained.

Manufacturing processes should be controlled and documented, and at some logical processing step, as determined by the manufacturer, GMP practices as described in this Guide should be applied and maintained. As the excipient manufacturing process progresses, the degree of assurance concerning the quality of the product should increase.

Justification based on a documented risk assessment and a thorough knowledge of the process is required to determine the point at which GMP should be applied. This is usually well before the final finishing operation and for example may be identified using methods such as HACCP (Hazard Analysis and Critical Control Point), FMEA (Failure Mode and Effects Analysis) or a detailed process flow diagram. Consideration should also be given to other factors such as batch *versus* continuous processing, dedicated *versus* multi-purpose equipment, open *versus* closed processes (see also Appendix A for further examples).

4 QUALITY MANAGEMENT SYSTEM - EXCIPIENT QUALITY SYSTEMS

4.1 General Requirements

The principles outlined in this Guide provide a comprehensive basis for the quality management system used in the manufacture of excipients. Excipient manufacturers should identify and implement the quality management processes required to assure excipient quality accounting for legal, technological, cultural and social environments. The elements of the quality management processes should be applied in a manner that is appropriate and proportionate to each of the product lifecycle stages, recognizing the different goals and knowledge available at each stage.

Where manufacturing, testing or other operations that could affect excipient quality are outsourced, this should be communicated to the customer (see also 7.2.3). The responsibility for quality remains with the excipient manufacturer and control measures should be defined (see also 7.4.2).

4.2 Documentation Requirements

4.2.1 General

The excipient manufacturer should have a system in place to control documents and data that relates to the requirements of the quality management system. The organization's overall intentions and approach to GMP should be described and documented to facilitate common understanding and consistent application.

4.2.2 Quality Manual

The excipient manufacturer should have a documented description of the quality management system, the quality policy and the commitment of the organization to applying the appropriate GMP and quality management standards contained in this Guide. This document should include the scope of the quality management system, reference to supporting procedures and a description of the interaction between quality management processes. Documentation should identify and justify the point where the full excipient GMP requirements of this Guide apply to each manufacturing process.

4.2.3 Control of Documents

The excipient manufacturer should establish and maintain procedures for the identification, collection, indexing, filing, storage, security, maintenance and disposition of controlled documents, including regulatory documents and documents of external origin that are part of the quality management system.

Procedures used in the manufacture of excipients should be documented, implemented and maintained. In addition, there should be formal controls relating to procedure approval, revision and distribution. These controls should provide assurance that the current version of a procedure is being used throughout the operational areas and previous revisions of documents have been removed.

Documents and subsequent changes to documents should be reviewed and approved by designated qualified personnel before issuance to the appropriate areas, as identified in the documents. Documents that impact product quality should be reviewed and approved by the quality unit (see also 5.5.1).

Controlled documents should include a unique identifier, date of issue and revision number to facilitate identification of the most recent document. Documents that impact product quality should have a defined owner. The department with the responsibility for issuing the documents should be identified. Where practical, changes and the reasons for the change should be documented.

Current versions of applicable documents should be available at points of use. Procedures should exist to prevent unintended use of obsolete documents and to apply suitable identification to them if they are retained for any purpose.

If a regulatory filing exists, such as an excipient DMF or CEP, procedures should exist for their appropriate periodic review and update.

Electronic documentation should meet the requirements for the document control system stated above. If electronic signatures are used on documents, they should be controlled to provide equivalent security to that given by a hand written signature. Electronic documents and signatures may also need to satisfy local regulatory requirements.

4.2.4 Control of Records

The excipient manufacturer should establish and maintain procedures for the identification, collection, indexing, correction, filing, storage, security, maintenance and disposition of records.

Records should be maintained to demonstrate achievement of the required quality and the effective operation of the quality management system. Records should be legible and identifiable with the product involved. The organization should define which records, results and reports of subcontractor activities are retained and by whom.

Entries in records should be clear, indelible, made directly after performing the activity (in the order performed), signed and dated by the person performing the observed task (unless otherwise justified). Corrections to entries should be signed and dated, leaving the original entry legible.

Measures should be taken to maintain data integrity at all times. For example, analytical results and calculations should be traceable to original data and measurements. Data integrity requirements apply equally to manual (paper) and electronic data. The inherent risks to data integrity may differ depending upon the degree to which data (or the system generating or using the data) can be configured, and therefore potentially manipulated.

Records should be kept for a defined period which should be appropriate to the excipients or as specified in local regulations, and at least one year past the expiry or re-evaluation date. If no expiry or re-evaluation date is stipulated, retention should be 5 years. Records should be stored and maintained in such a manner that they are readily retrievable, in facilities that provide a suitable environment to minimise deterioration or damage.

Certificates of analysis or certificates of conformity should have documented control procedures.

Electronic records should be subject to the same controls as those required for other records. Consideration should be given to the integrity and audit trail of electronically retained data. Where used, electronic signatures must be authenticated and secure, and comply with relevant regulatory requirements.

4.3 Change Control

For Guidance refer to the current version of the International Pharmaceutical Excipient Council Significant Change Guide for Pharmaceutical Excipients.

The excipient manufacturer should establish and maintain documented procedures to evaluate and approve changes that may have an impact on the quality of the excipient, including the impact on any regulatory submissions made by the excipient supplier or user. For example, this may include changes to:

- site of manufacture,
- scale of manufacture,
- production equipment,
- production process,
- packaging, labelling and documentation,
- raw materials for the manufacture of the excipient,
- excipient specifications and test methods,
- supply chain,
- computerized systems.

Evaluation and approval of changes should occur prior to the implementation. The quality unit should 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 should be communicated to customers and, as applicable, regulatory authorities. Records of the change control process should be retained. The impact of changes on processes, systems and activities should be assessed.

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

5 MANAGEMENT RESPONSIBILITY

5.1 Management Commitment

Top management should demonstrate their commitment to the quality management system and be accountable for its effectiveness. This should be accomplished through the development of a quality policy and establishment of quality and GMP objectives. Applicable statutory and regulatory requirements should be determined and met.

Top management should ensure that the quality policy, GMP objectives, and the definition of roles, responsibilities and authorities are communicated, understood and applied within the whole organization. They should ensure that the quality management system achieves its intended result and should promote continual improvement. Progress towards the documented quality objectives should be reviewed at planned intervals.

5.2 Customer Focus

Top management should ensure that customer requirements related to GMP and other matters are determined and, if applicable, agreed with the customer and met.

The excipient manufacturer should demonstrate to the customer the effectiveness of their quality management system. This may be by audit, third party certification, or other means.

5.3 Quality Policy

Top management should demonstrate its commitment to the quality policy and appropriate GMP, and ensure that it is communicated and implemented within the operational unit. The quality policy should support continual improvement of the quality management system. Management should participate in the development of the company's quality policy and provide the resources necessary for its development, maintenance and deployment.

5.4 Planning

5.4.1 Quality Objectives

Top management should set appropriate objectives for adherence to GMP to ensure that the excipient manufacturer maintains and improves its performance. These objectives should be deployed throughout the organization and should be measurable and consistent with the quality policy.

5.4.2 Quality Management System Planning

Top management should provide adequate resources to ensure conformance to the provisions of this Guide. There should be a process for the identification of resources needed for adherence to GMP. A gap analysis based on audits by internal personnel, customers, regulatory agencies or outside contractors and this Guide could be used for the purpose of identifying resource requirements.

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

5.5 Responsibility, Authority and Communication

5.5.1 Responsibility and Authority

Responsibility and authority should be clearly defined by top management and communicated within the organization.

It should be the responsibility of a quality unit or other appropriate unit, independent of production, to:

- ensure quality-critical activities are identified and undertaken as defined,
- approve suppliers of quality-critical materials and services,
- approve or reject raw materials, packaging components, intermediates and finished excipients, according to current approved specifications,
- ensure that there is a review of production records,
- ensure that where errors or deviations have occurred or are identified in the review process, they are fully investigated and documented,
- ensure corrective and preventative actions are implemented and effective,
- participate in reviewing and authorising significant changes that potentially affect quality (see also 4.3),
- review and approve the results of investigations into deviations from production instructions, test or measurement failures, and complaints,
- retain responsibility for approval or rejection of the excipient if it is produced, processed, packaged or held under contract by another company,
- develop and implement an internal audit programme of the quality management system,
- ensure that providers of outsourced services comply with the relevant sections of this Guide.

The excipient manufacturer may delegate some of the quality unit's activities to other personnel if appropriate controls (for example periodic audits, training and documentation) are in place and documented.

An organization chart by function should show inter-departmental relationships as well as relationships to top management of the company. Personnel who have an impact on excipient quality should have job descriptions.

5.5.2 Management Representative

The excipient manufacturer should appoint a management representative with sufficient authority to ensure that the provisions of this Guide are properly implemented. The representative should periodically report to top management on conformance to the quality management system, including changing customer and regulatory requirements.

5.5.3 Internal Communication

The excipient manufacturer should ensure appropriate systems are established to communicate GMP and regulatory requirements, quality policies, quality objectives and procedures throughout the organization. The communication should also provide information about the effectiveness of the quality management system.

Top management should be notified promptly of quality-critical situations, such as product retrievals, in accordance with a documented procedure.

5.6 Management Review

5.6.1 General

The top management of the company should hold periodic reviews of the quality management system to confirm the organization's continued conformance to this Guide.

The review should be recorded and include assessing opportunities for improvement and the need for changes to the quality management system. Such changes should be assessed and implemented via the change control procedure (4.3).

5.6.2 Review Input

Management review inputs should include for example:

- results of internal and external audits,
- customer feedback of the company performance,
- product conformity and process performance,
- action items from the previous management review,
- customer complaints,
- status of corrective or preventative actions,
- changes that could affect the quality management system,
- new, revised, or proposed regulatory requirements.

5.6.3 Review Output

The management review should identify the resources needed and opportunities presented for improvement of the quality management system and improvement of product conformance to customer and regulatory requirements. A record should be made of actions recommended and taken.

6 RESOURCE MANAGEMENT

6.1 Provision of Resources

The organization should determine and provide the required qualified personnel and resources (for example equipment, materials, buildings and facilities) to implement, maintain and improve the quality management system and to produce, package, test, store and release each excipient in a manner consistent with this Guide.

6.2 Human Resources

6.2.1 General

Personnel performing work affecting the quality of excipients should have the appropriate combination of education, training and experience for their assigned tasks. These requirements and tasks should be defined in the job description (5.5.1).

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

6.2.2 Competence, Awareness and Training

The excipient manufacturer should establish and maintain procedures for identifying training needs and providing the necessary training to personnel performing activities affecting excipient quality (including external and contract personnel), prior to performing those activities. Appropriate records of training should be maintained. Training should address the particular operations that the employee performs and GMP as it relates to the employee's functions.

Retraining requirements should be assessed and determined. Qualified individuals should conduct GMP training with sufficient frequency to ensure that employees remain familiar with applicable GMP principles, including data integrity. Management should establish adequate and continued personal hygiene training for personnel who handle materials so that they understand the precautions necessary to prevent contamination of excipients.

The training programme should ensure personnel understand that deviations from procedures may have an impact on the customer's product quality.

6.2.3 Personnel Hygiene

To protect excipients from contamination, the organization should conduct a documented risk assessment to identify areas in which the excipient is at risk of contamination from personnel or their activities. Only authorised personnel should enter those areas of the buildings and facilities designated as limited access areas.

Where identified, personnel should wear clean clothing suitable for the activity in which they are involved, and this clothing should be changed when appropriate. Requirements for additional protective apparel, appropriate to the duties performed, may include head, face, hand and arm coverings. Jewellery and other loose items, including those in pockets, should be removed or covered.

Personnel should practice good sanitation and health habits. Any person shown to have an apparent illness or open lesions (by either medical examination or supervisory observation) that may adversely affect the safety or quality of the excipient should be excluded from direct contact with raw materials, packaging components, intermediates and finished excipients until the condition is corrected or determined by competent personnel not to jeopardise the safety or quality of the excipient. Personnel should be instructed to report to supervisory personnel any health conditions that may have an adverse effect on excipients.

The storage and use of food, drink, personal medication, tobacco products or similar items should be restricted to certain designated locations separate from manufacturing areas.

6.3 Infrastructure

The infrastructure should be designed, managed, operated, cleaned and maintained in accordance with GMP principles to ensure excipient quality and to avoid contamination (including, where critical to excipient quality, control of particulate matter, microbiological control and control of water quality).

A documented risk assessment should be conducted, based on the intended use of the infrastructure, to identify areas in which the excipient is at risk of contamination from deficiencies in buildings and/or facilities.

6.3.1 Buildings and Facilities

The prevention of contamination should be considered in the design of the manufacturing processes and facilities, particularly where the excipient is exposed. Buildings and facilities used in the production, processing, packaging, testing or storage of an excipient should be maintained in a good state of repair and should be of suitable size, construction and location to facilitate cleaning, maintenance and correct operation appropriate to the type of processing.

Manufacturing processes associated with the production of highly sensitising or toxic products (for example herbicides, pesticides) should be located in dedicated facilities or use equipment separate from that used for excipient manufacture. If this is not possible then appropriate measures (for example cleaning, inactivation) should be implemented to avoid cross-contamination. The effectiveness of these measures should be demonstrated.

Where such activities are conducted, there should be adequate facilities for the sampling and testing of raw materials, packaging components, intermediates and finished excipients.

6.3.2 Equipment

Equipment used in the production, processing, packaging, testing or storage of an excipient should be maintained in a good state of repair and should be of suitable size, construction and location to facilitate cleaning, maintenance and correct operation, depending on the type of processing (for example batch *versus* continuous). Special consideration of the risk of breakage or damage should be given where glass equipment is utilised.

Equipment should be commissioned before use to ensure that it is functioning as intended.

The use, cleaning and maintenance of quality critical equipment should be recorded. The status of equipment should be readily identifiable by appropriate means.

Where equipment is located outdoors there should be suitable control to minimise the risk to excipient quality from the environment (for example processing within a closed system).

6.3.2.1 Equipment Construction

Process equipment should be constructed so that contact surfaces will not be reactive, additive or absorptive and thus not alter the quality of the excipient. Substances required for operation, such as lubricants or coolants, should preferably not come into contact with raw materials, packaging materials, intermediates or finished excipients. Where contact with such substances is possible, substances suitable for use in food applications should be utilised.

Equipment should be designed to minimise the possibility of contamination caused by direct operator contact in activities such as the unloading of centrifuge bags, use of transfer hoses (particularly those used to transfer powders) and the operation of drying equipment and pumps. The sanitary design of transfer and processing equipment should be evaluated. Equipment with moving parts should be assessed with regard to the integrity of seals and packing materials to control the risk of contamination.

6.3.2.2 Equipment Maintenance

Documented procedures should be established and followed for maintenance of critical equipment used in the production, processing, packaging, testing or holding of the excipient. There should be records of the use and maintenance of quality-critical equipment. These records can be in the form of a log, computer database or other appropriate documentation.

6.3.2.3 Computer Systems

Computer systems that may impact upon excipient quality should have sufficient controls for operation and maintenance and to prevent unauthorised access or changes to computer software, hardware or data, including:

- systems and procedures that show the equipment and software are performing as intended,
- procedures for checking the equipment at appropriate intervals,
- retention of accurate, suitable and regular back-up or archival systems such as copies of the programme and files,
- assurance that changes are traceable, verified and documented and only made by authorised personnel (see sections 4.2.4 and 4.3).

6.3.3 Utilities

Utilities (for example nitrogen, compressed air, steam) used in the production, storage or transfer of materials that could impact excipient quality should be assessed and appropriate action taken to control the risk of contamination and cross-contamination.

6.3.4 Water

Water used in the manufacture of excipients should be demonstrated to be of a suitable quality for its intended use. Unless otherwise justified, process water should, at a minimum, meet WHO guidelines for drinking (potable) water quality.

If drinking (potable) water is insufficient to ensure quality, or tighter chemical and/or microbiological water quality specifications are required, appropriate controls and specifications should be set, for example physical and chemical attributes, total microbial counts, limits on objectionable organisms and/or endotoxins.

Where water used in the process is treated by the manufacturer to achieve a defined quality the treatment process should be specified and monitored with appropriate action limits.

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

If interruptions in supply or deviations in the quality of such water occur, return to service should not occur until it is confirmed that the quality of the water has been restored. Appropriate evidence and rationale should be documented to show such interruptions have not compromised the quality of the excipient.

6.4 Work Environment

Where the excipient is exposed during manufacture it should be in an appropriate environment to minimise contamination, including cross contamination. A documented risk assessment should be carried out to determine the necessary controls.

The documented risk assessment should cover the following controls, as applicable:

- air handling systems,
- need for special environments,
- cleanliness and sanitary conditions,
- pest control,
- waste segregation and disposal.

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

6.4.1 Air Handling

Where the documented risk assessment has identified the need for an air handling system, the excipient manufacturer should demonstrate its effectiveness.

Excipient production unit air handling systems should be designed to prevent contamination and cross-contamination. For dedicated areas processing the same excipient it is permissible to recycle a portion of the exhaust air back into the same area. The adequacy of such a system for multi-use areas, especially if several products are processed simultaneously, should be assessed for potential cross-contamination.

6.4.2 Controlled Environment

A controlled environment may be necessary to avoid contamination or degradation caused by exposure to heat, air or light. The degree of protection required may vary depending on the stage of the process.

Where the documented risk assessment has identified the need for a controlled environment it should be monitored to demonstrate effectiveness and ensure product quality (for example inert atmosphere or protection from light). Where an inert atmosphere is required, the gas should be treated as a raw material. If interruptions to the controlled environment occur, adequate evidence and appropriate rationale should be documented to show that such interruptions have not compromised the quality of the excipient. Such environmental concerns become increasingly important as the process proceeds to the final product.

6.4.3 Cleaning and Sanitary Conditions

Adequate cleanliness is an important consideration in the design of excipient manufacturing facilities. Buildings used in the production, processing, packaging or holding of an excipient should be maintained in an appropriately clean and sanitary condition according to the type of processing conducted (for example open/closed systems).

Where maintenance of clean and sanitary conditions is critical to excipient quality, documented procedures should assign responsibility for cleaning and sanitation, describing in sufficient detail the cleaning schedules, methods, equipment and materials to be used in cleaning the buildings and facilities. These procedures should be followed and cleaning should be documented.

Where disinfectants and/or detergents are required for cleaning, a documented risk assessment should be used to determine their suitability.

6.4.4 Pest Control

Buildings should be free from infestation by rodents, birds, insects and other vermin.

Risk assessment may be used to determine specific pest control requirements. This assessment may be carried out by a specialist contractor. The excipient manufacturer should document the pest control programme. The use of suitable rodenticides, insecticides etc. should be documented. Where a service provider is utilised, there should be a contract in place (7.4.2).

Some raw materials, particularly botanicals, may contain some unavoidable contamination, such as rodent or other animal filth or infestation. The manufacturer should have sufficient control methods to prevent the increase of such contamination or infestation in holding areas and its spread to other areas of the plant.

6.4.5 Lighting

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

6.4.6 Drainage

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

6.4.7 Washing and Toilet Facilities

Adequate personnel washing facilities which ensure suitable hygiene standards can be maintained should be provided, including hot and cold water, soap or detergent, air dryers or single service towels. Clean toilet facilities should be separate from but easily accessible to working areas. Facilities for showering and/or changing clothes should be provided, where identified in the documented personnel hygiene risk assessment (see 6.2.3).

6.4.8 Waste

Waste should be segregated, labelled as appropriate, and disposed of in a manner appropriate to its type (e.g. chemical, biological, hazardous). Waste should be disposed of in a timely manner. If waste is not disposed of immediately, it should be suitably identified and stored.

7 PRODUCT REALISATION

7.1 Planning of Product Realisation

The excipient manufacturer should plan and develop the processes and controls needed for product manufacture.

These plans and controls should be appropriate to the production process, excipient specification, equipment and facilities used in the manufacture of the product.

Key aspects of the planning of a suitable process and its controls should include as appropriate:

- documented testing programmes for quality-critical materials including intermediates and excipients that include appropriate specifications, sampling plans, test and release procedures,
- generation and maintenance of records (see also 4.2.4) that provide evidence that these plans have been realised as intended and that enable traceability to be demonstrated (see also 7.5.3.1),
- provision of resources to implement these plans and controls,
- environmental and hygiene control programmes to minimise the risk of contamination,
- documented procedures describing activities related to the storage and distribution of excipients,
- actions from relevant documented risk assessments.

7.2 Customer-related Processes

7.2.1 Determination of Requirements Related to the Product

The excipient manufacturer should determine the excipient quality, labelling and delivery requirements of the customer. Additional requirements, whether customer-specific, legal or regulatory, should be considered.

This may include:

- compendial general requirements,
- TSE/BSE,
- residual solvents,
- elemental impurities,
- impurities originating from raw materials of natural origin, e.g. mycotoxins, pesticide residues.

Requirements not stated by the customer but necessary for specified or intended use, where known, should also be considered.

The above requirements may be laid down in a quality agreement. For guidance refer to the current version of the IPEC Quality Agreement Guide and Templates.

Revision to the agreed upon requirements may be initiated by either party (see also 4.3 and 7.2.2).

7.2.2 Review of Requirements Related to the Product

The excipient manufacturer and customer should mutually agree upon the requirements identified in 7.2.1 before supply commences. The manufacturer should have the facility and process capability to meet consistently the mutually agreed specifications. Where the requirements determined in 7.2.1 are changed, this review should be repeated before supply recommences.

7.2.3 Customer Communication

There should be processes in place:

- for provision of accurate and pertinent information to the customer, which may include controlled documents (see also 4.2.3),
- for provision of replies to customer enquiries, contracts and order handling requirements,
- to communicate the origin and traceability of the excipient to the customer,
- to inform customers of issues detected after delivery of the excipient (see also 8.3),
- to document and respond appropriately to customer complaints and feedback,
- to notify customers of significant changes (see also 4.3).

For additional change notification information refer to the current version of the International Pharmaceutical Excipient Council Significant Change Guide for Pharmaceutical Excipients.

7.3 Design and Development

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

GMP requirements as defined in this document are not always applicable in full during the design and development of new excipients and/or manufacturing processes. However, development batches of excipients that are intended for use in drug products should be manufactured in accordance with the applicable provisions of this Guide.

7.4 Purchasing

7.4.1 Purchasing Process

Risk assessment may be used to determine quality critical materials and services (for example subcontract manufacturers and laboratories). Excipient manufacturers should have a documented system for selection and approval of suppliers. Supplier approval is the responsibility of the quality unit based on a documented evaluation of the supplier's quality management system, including adequate evidence that they can consistently meet agreed requirements. This may require periodic audits of the supplier's manufacturing facility. Records of these activities should be maintained.

Materials should be purchased against an agreed specification from approved suppliers.

7.4.2 Purchasing Information

Purchasing agreements should describe the material or service ordered including, where critical to excipient quality, the following:

- the name, type, class, grade, item code number or other precise identification traceable to the raw material and packaging specifications,
- drawings, process requirements, inspection instructions and other relevant technical data, including requirements for approval or qualification of product, procedures, process equipment and personnel,
- adherence to the appropriate sections of this Guide for relevant contract manufacturers or laboratories,
- a statement to notify the excipient manufacturer of significant changes in quality-critical raw materials.

7.4.3 Verification of Purchased Product

There should be procedures for control of incoming goods describing the approval and release of quality-critical material.

Upon receipt, quality-critical materials should be placed in quarantine and should not be used prior to release. Effective quarantine can be established with suitable identifying labels, signs and/or other manual documentation systems. When quarantine and stock control are managed with computer systems *in lieu* of a physical stock control, then system controls should prevent the use of unreleased material.

Quarantine may not be feasible for materials supplied via pipelines. In these cases, the excipient manufacturer should establish an agreement with the supplier so that they are notified of material that does not meet specification.

Sampling activities should be conducted under defined conditions, in accordance with a defined sampling method and using procedures and sampling tools designed to prevent contamination and cross-contamination.

Quality-critical materials used in the manufacture of an excipient should be tested or otherwise verified prior to use. Verification should include availability and a check of the supplier certificate of analysis and, wherever feasible, at least an identification test. Testing schedules should be organised to separate those tests that are routine from those that are performed infrequently or only for new suppliers.

Bulk deliveries should have additional controls to ensure material purity and freedom from contamination (for example dedicated tankers, tamper-evident seals, a certificate of cleaning, analytical testing and/or audit of the supplier).

These procedures, activities and results should be documented.

7.5 Production and Service Provision

7.5.1 Control of Production and Service Provision

Production activities should be carried out under controlled conditions (see also section 7.1).

Specific examples of important controls, some of which may not be applicable to all excipient manufacturers, are illustrated in the following sections.

7.5.1.1 Production Instructions and Records

Production instructions and records are required but may differ for the type of operation, for example batch *versus* continuous processes.

There should be a controlled document that describes how the excipient is produced (for example master production instructions, master production and control records, process definitions etc.).

For batch processes an accurate reproduction of the appropriate master production instructions should be issued to the production area. For continuous processes a current processing log should be available.

Records should be available for each batch of excipient produced and should include complete information relating to the production and control of each batch. For continuous processes the batch and its records should be defined (for example based on time or defined quantity). Records may be in different locations but should be readily retrievable.

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

- date/time each step was completed,
- a log of key parameters together with conformance check against specified operating ranges,
- identification of persons (e.g. initials traceable to signature log) performing and directly supervising or checking each significant step, operation or control parameter,
- identification of major equipment and lines used,
- material inputs to enable traceability, for example batch number and quantities of raw material/intermediate, time it was added, etc.,
- in-process and laboratory control results,
- the quantity produced for the defined batch and a statement of the percentage of theoretical yield, unless not quantifiable (for example as in some continuous processes),
- inspection of the packaging and labelling area before and after use,
- labelling control records,

- description of excipient product containers and closures,
- description of sampling performed,
- failures, deviations and their investigations,
- results of final product inspection.

7.5.1.2 Equipment Cleaning

Risk assessment may be used by the manufacturer to design and justify cleaning and sanitisation procedures. Evidence of their effectiveness should be provided based on pre-determined acceptance criteria. In multi-purpose plants the use of the "model product approach" (groups of product of similar type) may be used in justifying a suitable procedure.

Cleaning and sanitisation procedures should be documented. They should contain sufficient detail to allow operators to clean each type of equipment in a reproducible and effective manner (see also 6.4.3). There should be a record confirming that these procedures have been followed.

Equipment and utensils where critical to excipient quality should be cleaned and sanitised at appropriate intervals to prevent contamination and cross-contamination of the excipient. The rationale for these intervals should be documented.

Where disinfectants and/or detergents are required for cleaning, an assessment of their suitability should be documented.

The cleanliness status of equipment should be readily identifiable and recorded.

Where multi-purpose equipment is in use it is important to be able to determine previous usage when investigating cross-contamination or the possibility of such contamination (see also 7.5.1.7).

During a production campaign incidental carry-over frequently occurs and is acceptable usually since clean-up between successive batches of the same excipient is not normally required to maintain quality levels.
Products that leave residues that cannot be effectively removed should be produced in dedicated equipment.

7.5.1.3 Recovery of Solvents, Mother Liquors and Second Crop Crystallisations

The use of recycled or recovered materials containing recoverable amounts of excipient, reactants or intermediates should be justified. Where materials are recovered and reused in the same process or different processes they should meet appropriate specifications prior to reuse or mixing with other approved material.

Such processes should be documented in the production records or logs to enable traceability.

7.5.1.4 Blending or Mixing

Blending or mixing to ensure batch uniformity or to facilitate processing should be controlled and documented. If the intent of the operation is to ensure batch

uniformity it should be performed so as to ensure homogenous mixing of materials to the extent feasible and should be reproducible from batch to batch.

Other acceptable blending operations for finished excipients include, but are not limited to:

- blending of small batches to increase batch size,
- blending of tailings (i.e., relatively small quantities of isolated material) from batches of the same excipient to form a single batch.

The blending process should be documented and should allow traceability back to the individual batches that make up the blend.

Blending processes should be adequately controlled to ensure homogeneity of the combined batch.

The blended batch should be tested for conformance to established specifications. The expiry or re-evaluation date of the blended batch should be justified.

See also 8.3 Control of Nonconforming Product.

7.5.1.5 In-process Control

In-process inspection, sampling and testing should be performed according to documented procedures. In-process controls may be based upon monitoring the process or actual sample analysis at defined locations and times.

In-process samples should be clearly labelled and not returned to production for incorporation into the final batch.

The results of in-process controls should be recorded and should be verified against established process parameters or acceptable tolerances. Work instructions should define the procedure to follow and how to utilise the inspection and test data to control the process. These work instructions should include defined actions to be taken when the results are outside specified limits. Where approval to continue with the process is issued within the production department, the specified tests should be performed by trained personnel and the results recorded.

7.5.1.6 Packaging and Labelling

Procedures should be employed to protect the quality and purity of the excipient when it is packaged and to ensure that the correct label is applied to all containers. Packaging and labelling operations should be designed to prevent mix-ups.

Procedures should be implemented to ensure that the correct labels are printed and issued and that the labels contain the correct information. The information on the label should be indelible. The procedure should also specify that excess labels are immediately destroyed or returned to controlled storage. Excess labels bearing batch numbers should be destroyed. Packaging and labelling facilities should be inspected immediately before use to ensure that materials that are not

required for the next packaging operation have been removed. The outcome of the inspection should be recorded.

Where excipients are labelled on the packaging line, packaged in pre-printed bags or shipped in bulk containers there should be documentation of the system used to satisfy the intent of the above procedures.

Repackaging / relabelling activities should follow the principles outlined in the IPEC Good Distribution Practices Guide, Chapter 7.

7.5.1.7 Records of Equipment Use

Records of quality-critical equipment use should be retained. These records should allow the sequence of cleaning, maintenance and production activities to be determined.

7.5.2 Validation of Processes for Production and Service Provision

The concept of process validation is a key element in ensuring that the excipient manufacturing process is capable of consistently producing an excipient that is meeting its specifications.

The full validation programme that is typically performed in the pharmaceutical industry may not always be carried out by the excipient manufacturer; however, product testing alone may not be sufficient to reveal variations that may have occurred.

The excipient manufacturer should demonstrate the consistent operation of the manufacturing process based on knowledge of process parameters, product attributes and their inter-relationship.

Knowledge of the process may be based on, e.g. process capability studies, development and scale-up reports, periodic product reviews.

After significant changes, the impact on process capability should be assessed and documented.

7.5.3 Identification and Traceability

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

Documents that facilitate traceability, e.g. CoAs should be provided for each delivery as agreed with the customer.

7.5.3.1 Traceability

Quality-critical items should be clearly identified and traceable through records. These records should allow traceability of the excipient both upstream and downstream. Identification of raw materials used in batch production processes should be traceable through the batch numbering system or other appropriate system. Identification of raw materials used in excipients produced by continuous processing should indicate the timeframe during which a particular batch of raw material was processed through the plant.

Raw materials, including solvents, are sometimes stored in bulk tanks or other large containers, making precise separation of batches difficult. Nevertheless, the use of such materials should be documented in production records.

7.5.3.2 Inspection and Test Status

There should be a system to identify the inspection status of quality-critical items including raw materials, packaging materials, intermediates and finished excipients. Whilst storing materials in identified locations is preferred, any means that clearly identifies the test status is satisfactory. Continuously-fed materials may need special consideration in order to satisfy these requirements.

7.5.3.3 Labelling

Labelling for excipient packages is subject to national and international regulatory requirements, which may include transportation and safety measures. As a minimum, labels should include:

- the name of the excipient and grade if applicable,
- the excipient manufacturer's and/or distributor's name and address,
- the batch number from which the complete batch history can be determined,
- special storage conditions, if applicable.

7.5.4 Customer Property

The excipient manufacturer should establish and maintain procedures for verification, storage and maintenance of customer-supplied materials intended for incorporation into the customer's excipient. Verification by the manufacturer does not relieve the customer of the responsibility to provide an acceptable material. Material that is lost, damaged or is otherwise unsuitable for use should be recorded and reported to the customer. In this case, procedures should be in place for acceptable disposition and replacement of the material. The manufacturer should also make provisions to protect other real and intellectual property that is provided by the customer (for example test equipment, test methods and specifications).

7.5.5 Preservation of Product

7.5.5.1 Handling, Storage and Preservation

Excipients, intermediates and raw materials should be handled and stored under appropriate conditions of temperature, humidity and light according to documented procedures so that their quality is not affected.
Storage containers should be identified and labelled with their contents.

Outdoor storage of raw materials (for example acids, other corrosive substances or explosive materials) or excipients is acceptable provided the containers give suitable protection against deterioration or contamination of their contents, identifying labels remain legible and containers are adequately cleaned prior to opening and use.

Records of storage conditions should be maintained if they are critical for the continuing conformance of the material to specification. Where applicable, deviations from such specified storage conditions should be assessed.

For more details on storage and warehousing practices refer to the current version of the IPEC Good Distribution Practices Guide.

7.5.5.2 Packaging Systems

The selection of excipient packaging systems should be justified, documented and should include the following features:

- documented specifications, based on an excipient's properties and stability,
- incoming inspection and / or testing methods,
- tamper-evident seals, where feasible,
- containers that provide adequate protection against deterioration or contamination of the excipient during transportation and recommended storage,
- containers that do not interact with or contaminate the excipient,
- storage and handling procedures which protect containers and closures and minimise the risk of contamination, damage or deterioration and which will avoid mix-ups (for example between containers that have different specifications but are similar in appearance).

If returnable excipient containers are reused, previous labelling should be removed. If the containers are repetitively used solely for the same excipient, previous batch numbers or the entire label should be removed or completely obliterated.

Where containers are reused, verified cleaning procedures should be in place and cleaning / sanitisation records should be maintained.

7.5.5.3 Delivery and Distribution

Excipients should only be supplied within their expiry and/or retest period.

Identification and traceability of quality-critical aspects are required of excipient manufacturers. Distribution records of excipient shipments should be kept. These records should be identified by excipient batch, where and to whom the excipient was shipped, the amount shipped and the date of shipment so as to facilitate retrieval if necessary. Where excipients are handled by a series of different distributors, it should be possible to trace them back to the original manufacturer and not just to the previous supplier.

The manufacturer should maintain the integrity and the quality of the product after final inspection and test. Where contractually specified, this protection should be extended to include delivery to the final destination.

Suppliers of transport services should be provided with the applicable transport conditions in order for them to maintain required conditions. For more details on distribution practices refer to the current version of the IPEC Good Distribution Practices Guide.

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

7.6 Control of Measuring and Monitoring Devices

Measuring and test equipment, including computerised systems, identified as being quality-critical should be qualified / calibrated and maintained. This includes in-process instruments as well as test equipment used in the laboratory. The control programme should include the

standardisation or calibration of instruments and equipment at suitable intervals in accordance with an established documented programme. This programme should contain specific instructions, schedules, limits for accuracy and precision and provisions for remedial action in the event that accuracy and/or precision limits are not met. Calibration standards should be traceable to recognised national or Compendial standards as appropriate.

Instruments and equipment not meeting established specifications should not be used and an investigation should be conducted to determine the validity of the previous results since the last successful qualification / calibration. The current qualification / calibration status of quality-critical equipment should be known and verifiable to users.

8 MEASUREMENT, ANALYSIS AND IMPROVEMENT

8.1 General

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

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

8.2 Monitoring and Measurement

8.2.1 Customer Satisfaction

The excipient manufacturer should establish measurement activities to assess customer satisfaction. Such measurements can include customer complaints, return of excipients and customer feedback. This information should drive activities to continuously improve customer satisfaction.

8.2.2 Internal Audit

The excipient manufacturer should carry out a comprehensive system of planned and documented internal quality audits. These should determine whether quality related activities comply with planned arrangements and the effectiveness of the quality management system. Audits and audit frequency should be scheduled on the basis of the status and criticality of the activity. Selection of auditors and conduct of audits should ensure objectivity and impartiality of the auditors.

Audit results should be documented and discussed with management personnel having responsibility in the area audited. Management personnel responsible for the area audited should take corrective action on the nonconformities found.

Audits and follow-up actions should be carried out in accordance with documented procedures.

Appendix A, Auditing Considerations will be of assistance in establishing an internal audit programme.

8.2.3 Monitoring and Measurement of Processes

The excipient manufacturer should identify the tests and measurements necessary to adequately control manufacturing and quality management system processes. Where

critical to excipient quality, techniques that are used to verify that the processes are under control should be established.

Corrective action should be taken to ensure the excipient meets requirements when deviations from planned results occur.

Periodic reviews of key indicators such as process quality attributes and process failures should be conducted to assess the need for improvements.

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8.2.4 Monitoring and Measurement of Product

The excipient manufacturer should establish test methods and procedures to ensure the product consistently meets specifications.

All analytical methods should be fit for purpose. The analytical methods may be those included in the current edition of the appropriate pharmacopoeia or another accepted standard. However, the methods may also be non-Compendial.

If the excipient manufacturer claims that their product is in compliance with a pharmacopoeia or an official compendium, then:

- non-Compendial / in-house analytical tests should be demonstrated to be equivalent to those in the compendia,
- it should comply with applicable general chapters and notices.

The responsibility for monitoring the current pharmacopeia or official compendium should be assigned.

8.2.4.1 Laboratory Controls

Measures should be taken to maintain data integrity at all times.

The excipient manufacturer should have procedures in place to ensure data is authentic, complete and accurate; that it can be traced to its source and that it is readily available (see also 4.2.4).

Laboratory controls should include complete data derived from tests necessary to ensure conformance with specifications and standards, including:

- a description of the sample received for testing together with the material name, batch number or other distinctive code and date the sample was taken,
- a statement referencing each test method used,
- a record of raw data secured during each test including sample preparation, graphs, chromatograms, charts and spectra from laboratory instrumentation, identified to show the specific material and batch tested,
- a record of calculations performed in connection with the test,
- test results and how they compare with established specifications,
- a record of the person who performed each test and the date(s) the tests were performed,
- a record of the equipment used to perform the test, to ensure traceability to its qualification / calibration status (see also 7.6).

There should be documented procedures for the preparation, labelling, handling and storage of laboratory reagents and solutions.

Purchased reagents and solutions should be labelled by the supplier with the proper name, concentration and expiry date. Once opened the container should additionally be labelled with the remaining usage period.

Records should be maintained for solutions and / or reagents prepared internally and should include the identity of the solution / reagent, name of preparer, date of preparation and quantities of material used.

Volumetric solutions should be standardised according to an internal method or by using a recognised standard. Records of the standardisation should be maintained.

Where used, primary reference reagents and standards should be appropriately stored and need not be tested upon receipt provided that a certificate of analysis from the supplier is available. Secondary reference standards should be appropriately prepared, identified, tested, approved and stored. There should be a documented procedure for the qualification of secondary reference standards against primary reference standards. The re-evaluation period should be defined for secondary reference standards and each batch should be periodically re-qualified in accordance with a documented protocol or procedure.

8.2.4.2 Finished Excipient Testing and Release

Finished excipient testing should be performed on each batch to ensure that the excipient conforms to documented specifications. There should 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 should be responsible for the release of the finished excipient.

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 control records.

8.2.4.3 Out-of-Specification Test Results

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

Retest sample results may only be used to replace the original test result if a documented investigation concludes that the original result is erroneous due to an assignable root cause.

When there is no assignable root cause, the OOS procedure should define:

- criteria for retesting and the use of retest sample results,
- criteria for re-sampling.
- which statistical techniques are to be used and under what circumstances.

When statistical analysis is used, both the original and retest data must be included in the investigation and reported.

These same principles apply when the sample is suspected of not being representative of the material from which it was taken.

8.2.4.4 Retained Samples

A representative sample of each batch of the excipient should be retained, unless otherwise justified and documented. The retention period should be justified and based on the expiry or re-evaluation date.

The retained samples should be stored in a secured location, readily retrievable and in conditions consistent with the recommended storage conditions for the finished excipient.

The samples should be maintained in a packaging format that is equivalent to or more protective than the commercial packaging system.

Unless otherwise justified and documented, the sample size should be at least twice the amount required to perform complete specification testing.

8.2.4.5 Certificates of Analysis

The organization should provide certificates of analysis to the required specification for each batch of excipient. More details on the suitable contents of a certificate of analysis can be found in the IPEC Certificate of Analysis Guide for Pharmaceutical Excipients.

8.2.4.6 Impurities

Where possible, excipient manufacturers should identify and set appropriate limits for impurities. Limits should be based upon appropriate safety data, limits as described in official compendia or other requirements and sound GMP considerations. Manufacturing processes should be adequately controlled so that the impurities do not exceed such established limits.

Excipient manufacturers should conduct documented risk assessments in order to determine whether the excipient specifications should include tests and limits for elemental impurities, e.g. metal catalysts.

Many excipients are extracted from or purified using organic solvents. These solvents are normally removed by drying. It is important that excipient specifications include tests and limits for solvent residues.

Consideration should be given to the following:

- microbiological bioburden of the material, including levels and types of microorganisms likely to be present,
- impurities originating from raw materials of natural origin, e.g. mycotoxins, pesticide residues.

In some manufacturing processes insoluble and visible particles cannot be fully excluded. The excipient manufacturer should implement mitigation strategies based on documented risk assessment to maintain the occurrence of such particles at an acceptable level.
For guidance related to such “technically unavoidable particles” refer to the current version of the International Pharmaceutical Excipient Council TUPP Guide.

8.2.4.7 Stability

While many excipient products are stable and may not require extensive testing to assure stability, the stability of excipients is an important factor contributing to the overall quality of the drug product. For excipients that have been on the market for a long time historical data may be used to indicate stability.

More details can be found in the IPEC Excipient Stability Programme Guide.

8.2.4.8 Expiry/Re-evaluation Periods

An expiry or re-evaluation period should be assigned to each excipient and communicated to the customer.

8.3 Control of Nonconforming Product

Raw material, intermediate or finished excipient found not to meet specifications and / or the expected quality should be clearly identified and controlled to prevent inadvertent use or release for sale. A record of nonconforming product should be maintained. Incidences of nonconformance should be investigated according to a documented procedure in order to identify the root cause and to assess the potential impact on other batches / products and on processes and activities. The investigation should be documented and action taken to prevent recurrence.

Procedures should exist for the evaluation and subsequent disposition of nonconforming products. Nonconforming product should be reviewed in accordance with documented procedures to determine if it may be:

- reprocessed/reworked to meet the specified requirements,
- accepted by the customer with their agreement,
- re-graded for other applications,
- destroyed.

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

8.3.1 Reprocessing

Repetition of an activity that is a normal part of the manufacturing process (reprocessing) should only occur when it has already been assessed and documented that the excipient may be made in that manner. In all other cases, the guidance for reworking should be followed.

Records of reprocessing should be maintained.

8.3.2 Reworking

An activity that is not a normal part of the manufacturing process (reworking) should only be conducted following a documented review of risk to excipient quality and approval by the quality unit. As appropriate, when performing the risk assessment, consideration should 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,

- performance of the excipient,
- additional controls needed to minimise the risk to excipient quality.

The equivalence of the quality of reworked material to original material should also be evaluated and documented to ensure that the batch will conform to established specifications and characteristics.
Records of reworking should be maintained.

8.3.3 Returned Excipients

There should be a documented procedure detailing the process for handling returned goods.
Returned excipients should be identified and quarantined until the quality unit has completed an evaluation of their quality, considering the excipient's integrity and conformance to the required storage and / or transportation conditions throughout the supply chain. Returned excipients should only be considered for resale if this conformance is confirmed. Other factors may need to be considered, e.g. remaining shelf life.
Records for returned products should be maintained and should include the name of the excipient and the batch number, reason for the return, quantity returned and ultimate disposition of the returned excipient.

8.3.4 Retrieval / Recall

There should be a documented procedure defining how the retrieval of an excipient from distribution should be conducted and recorded. Retrieved materials should be identified and quarantined.

The effectiveness of the arrangements for recalls should be evaluated at regular intervals, e.g. by conducting a traceability exercise or "Mock" recall.

8.4 Analysis of Data

The excipient manufacturer should develop methods for evaluating the effectiveness of its quality management system and use those data to identify opportunities for improvement. Such data can be derived from customer complaints, product reviews, process capability studies, internal and customer audits. The analysis of such data may be used as part of the management review (see also 5.6).

A periodic review of key indicators such as product quality attributes, customer complaints and product nonconformities may be conducted to assess the need for improvements.

8.5 Improvement

8.5.1 Continual Improvement

The excipient manufacturer should take proactive measures to continuously improve manufacturing and quality management system processes. To identify opportunities for continual improvement, analysis of the following performance indicators may be considered:

- root causes of nonconforming products,
- results of internal and external audits,
- customer returns and complaints,
- process and operational failures.

8.5.2 Corrective Action

The excipient manufacturer should establish, document and maintain procedures for:

- determining the root causes of nonconformities,
- definition of corrective actions including assignment of responsibilities and timelines for implementation,
- ensuring that corrective actions are implemented and effective,
- implementing and recording changes in procedures resulting from corrective action.

8.5.3 Preventive Action

The excipient manufacturer should establish, document and maintain procedures for:

- initiating preventive actions including assignment of responsibilities and timelines for implementation, to deal with problems at a level corresponding to the risks,
- ensuring that preventive actions are implemented and effective,
- implementing and recording changes in procedures resulting from preventive action.

APPENDIX A AUDITING CONSIDERATIONS

A1. Introduction

Environmental conditions, equipment and operational techniques employed in excipient manufacture are often those of the chemical industry as opposed to the pharmaceutical industry. Chemical processes can produce impurities from side reactions. Careful process control is therefore essential to minimise levels of impurities and contamination.

Excipients are often manufactured on a large scale utilising continuous processing and automated process controls. Production equipment and processes vary depending on the type of excipient being produced, the scale of production and the type of operation (for example batch *versus* continuous process).

This appendix is intended to aid in the preparation by an excipient manufacturer for an audit. Both external and internal auditors (see also 8.2.2) will find this appendix useful in identifying the significant issues with respect to GMP and quality that require examination. This section will assist excipient manufacturers in identifying the key deliverables when adopting the GMP standards listed in the other sections of this Guide and help in planning an audit to verify the quality of the excipient manufacturing process and the quality management system.

For additional information on auditing refer to *The Joint IPEC-PQG Good Manufacturing Practices Audit Guideline for Pharmaceutical Excipients*. Also for guidance on the auditing process refer to the CQI PQG *Monograph No 5 Pharmaceutical Auditing*.

A2. GMP Principles

A2.1 Control of impurities and contamination

In general, the pharmaceutical customer does not perform further chemistry or purification steps on the excipient and it is used as purchased. Consequently, impurities present in the excipient are likely to be present in the drug product. Although dosage form manufacturers have some control over excipient quality through specifications, the excipient manufacturer has greater control over the physical characteristics, quality and the presence of impurities in the excipient they produce.

External contamination of the excipient can arise from the manufacturing environment. However, chemical processes used to manufacture excipients are often performed in closed systems that afford protection against such contamination, even when the reaction vessels are not located in buildings. The external environment may require suitable controls to avoid potential contamination wherever the excipient or in-process material is exposed.

A2.2 Excipient properties and functionality

Excipients are frequently used in different types of drug products where physical characteristics, such as particle size, may be important. While the finished dosage form manufacturer is primarily responsible for identifying the particular physical characteristics needed, it is also the responsibility of the excipient manufacturer to control excipient manufacturing processes adequately to ensure consistent conformance to excipient specifications. Wherever possible, consideration should be given to the end use of the excipient. This is particularly important if the excipient is a direct component of a sterile drug product or one that is claimed to be pyrogen-free.

A2.3 Consistency of manufacture and change control

A thorough understanding of the manufacturing process and effective control of change can best assure consistency of excipient quality from batch to batch. Implementation of changes may also have consequences for registration filings with regulatory agencies.

For detailed guidance refer to *The IPEC Significant Change Guide for Pharmaceutical Excipients*

A2.4 Traceability

Traceability of batch-related records to facilitate investigations and retrieval of product is also a key requirement of GMP.

A3. Application of GMP Principles

It is the responsibility of the excipient manufacturer to designate and document the rationale for the point in the manufacturing process at which appropriate GMP is to be applied. From this point on appropriate GMP should be applied. The manufacturer should apply a level of GMP to each manufacturing stage commensurate with the importance of that step in ensuring product integrity. This may be demonstrated by means of the use of a risk assessment procedure (for example HACCP, FMEA).

The stringency of GMP in excipient production should increase as the process proceeds from early manufacturing to final stages, purification and packaging. Physical processing (for example granulation, coating or physical manipulation of particle size such as milling, micronising) as well as chemical processing of excipients should be conducted at least to the standards suggested by this Guide.

It should be recognised that all intermediates might not require testing. An excipient manufacturer should, however, be able to identify critical or key points in the manufacturing process where selective intermediate sampling and testing is necessary in order to monitor process performance.

A4. General Auditing Considerations

Audits of an excipient operation will be influenced by the purpose of the audit and the intended use of the excipient. The key stages of a production process should be examined to determine whether the manufacturer adequately controls these steps so the process performs consistently. Overall, an audit should assess the excipient manufacturer's capability to deliver a product that consistently meets established specifications.

The audit team may consist of experienced personnel as appropriate to the scope and purpose of the audit. External auditors must respect confidentiality of the manufacturer’s processes and other disclosures.

It should be appreciated that in global organizations some functions may be centralised and hence may not be auditable at every manufacturing location (e.g. stability programmes, supplier approval, IT related activities, etc.).

An audit should focus on the quality-critical processing steps that are necessary to produce an excipient that meets the established physical, chemical and microbiological criteria. These steps

should be identified and controlled by the excipient manufacturer. Quality-critical processing steps can involve a number of unit operations or unit processes.

Quality-critical steps can include, but are not limited to, the following:

- phase changes involving the desired molecule, solvent, inert carrier or vehicle (for example dissolution, crystallisation, evaporation, drying, sublimation, distillation or absorption),
- phase separation (for example filtration or centrifugation),
- chemical changes involving the desired molecule (for example removal or addition of water of hydration, acetylation or formation of a salt),
- adjustments of the solution containing the molecule (for example pH adjustment),
- precise measurement of added excipient components, in-process solutions, recycled materials (for example weighing or volumetric measurements),
- mixing of multiple components,
- changes that occur in surface area, particle size or batch uniformity (for example milling, agglomeration or blending).

A5. Audit Check Points

A good approach for an excipient plant audit is a review of the following areas:

- physical walk through of manufacturing and supporting processes following material flow, nonconformances, such as the rejection of a batch that did not meet specifications, customer complaints, return of a product by a customer or retrieval of a product. The manufacturer should have determined the cause of the nonconformance, a report of the investigation prepared and subsequent corrective action initiated and documented. Records and documents should be reviewed to ensure that nonconformances are not the result of a poorly developed or inconsistent process,
- customer complaint files, such as reports that some aspect of the product is not entirely suitable for use, since these may be caused by impurities or inconsistencies in the excipient manufacturing process,
- change control logs to ascertain whether the company evaluates their significant changes to decide if the customer and/or regulatory authority should be notified,
- nonconforming products meeting or documents and/or equivalent records that demonstrate that the disposition of nonconforming product is handled in an appropriate manner by responsible individuals,
- master formula and production records for frequent revisions that may reveal problems in the excipient production process,
- evidence for the presence of unreacted intermediates and solvent residues in the finished excipient,
- materials management systems to ensure adequate control over nonconforming materials so they cannot be sold to customers or used in manufacturing without authorisation,
- review of a process flow diagram to aid understanding of the various processing stages. The critical stages and sampling points should be identified as part of the review of the processing records,
- review of contamination control measures,
- relevant documented risk assessments,
- data integrity aspects,
- training records.

In evaluating the adequacy of measures taken to prevent contamination and cross-contamination of materials in the process, it is appropriate to consider the following risk factors:

- the type of system (for example open or closed). Enclosed systems in chemical plants often are not closed when they are being charged and/or when the final product is being emptied. In addition, the same reaction vessels are sometimes used for different reactions,
- the form of the material (for example wet or dry),
- the stage of processing and use of the equipment and/or area (for example multi-purpose or dedicated),
- continuous *versus* batch production.

A6. Documentation and Record Review

As processing proceeds, it is important that a chain of documentation exists which includes:

- a documented process,
- the identification of critical processing steps,
- appropriate production records,
- records of initial and subsequent batch numbers,
- records of raw materials used,
- comparison of test results against meaningful standards,
- overview of any subcontracted operations.

If significant deviations from the normal manufacturing process are recorded there should be evidence of suitable investigations and a review of the quality of the excipient.

In order to promote uniformity in excipient GMP inspections the following basic requirements should be established:

- that a unique batch number is assigned to the excipient which enables it to be traced through manufacture to release and certification,
- that suitable controls are in place for the preparation of a batch record for batch processing and/or a production record, log sheet or other appropriate documentation for continuous processing,
- demonstration that the batch has been prepared using GMP guidelines from the processing point at which excipient GMP has been determined to apply,
- confirmation that the batch is not combined with material from other batches for the purpose of either hiding or diluting an adulterated batch,
- records showing that the batch has been sampled in accordance with a sampling plan that ensures a representative sample of the batch,
- records that the batch has been analysed using scientifically established test methods designed to assure that the product meets the established standards, specifications and characteristics.