# The Joint IPEC – PQG Good Manufacturing Practices Guide

***FOR PHARMACEUTICAL EXCIPIENTS***

**2006**

## FOREWORD

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.

In contrast to finished dosage forms and Active Pharmaceutical Ingredients (APIs), there are no specific GMP regulations for excipients. In addition, there are a large number of applications of this diverse range of materials which makes the development of excipient GMP guidelines challenging. However, there is a general expectation that excipients are manufactured to recognised GMP principles.

This document proposes GMP appropriate for the manufacture of excipients and is a joint initiative between the International Pharmaceutical Excipients Council (IPEC), as IPEC-Americas and IPEC Europe and the Pharmaceutical Quality Group (PQG), incorporating the IPEC Good Manufacturing Practices Guide for Bulk Pharmaceutical Excipients, 2001 with the PQG's PS 9100:2002 Pharmaceutical Excipients. During guide development, the opportunity was taken to make further clarifications of the text and to ensure alignment with the corresponding clauses in ISO 9001. The top-level headings in Sections 4 to 8 of this document match those in Sections 4 to 8 of ISO 9001 with the exception of Section 4.3 – Change Control. Sub headings have been expanded or reduced from the ISO 9001 structure to provide clarity of text.

This Guide makes an essential contribution to the wider understanding and attainment of good manufacturing practice appropriate for the excipient supply industry. Excipient manufacturers and their customers can be assured that excipients manufactured according to this Guide will meet internationally accepted good manufacturing practice principles.

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## ACKNOWLEDGEMENTS

This Guide was prepared by a team from The International Pharmaceutical Excipients Council (IPEC) and the Pharmaceutical Quality Group (PQG).

### 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.

For further information see www.ipec.org

### 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

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:

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# JOINT IPEC – PQG GOOD MANUFACTURING PRACTICE GUIDE FOR PHARMACEUTICAL EXCIPIENTS 2006

**This document represents voluntary guidance for the pharmaceutical 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**.

## 1 INTRODUCTION

### 1.1 Purpose and Scope

This document is an internationally accepted Guide that defines the extent and point of application of appropriate Good Manufacturing Practice (GMP) principles for excipient manufacture. The Guide 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. It will assist both auditors and manufacturers to establish whether the facilities and controls used for the manufacture of excipients are adequate and whether the excipients possess the quality and purity which they purport to possess and are suitable for their intended use.

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 can be consulted and adapted as necessary to the excipient in question.

The Guide does not address the specific GMP relating to Good Trade and Distribution Practices (GTDP). For additional guidance on GMP for distributors refer to the WHO *Good trade and distribution practices for pharmaceutical starting materials* (see also Appendix C).

### 1.2 Principles Adopted

#### 1.2.1 The Guide and its Use

Pharmaceutical 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.

The headings in this document have been aligned with the ISO 9001 clause numbers because many excipient manufacturers already use that 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 current ISO 9001 clauses.

IPEC and the PQG believe that merging GMP principles for pharmaceutical excipient manufacturing into the ISO 9001 quality management system enhances not only quality management but also an organisation’s operational procedures.

## 1.3 Document Structure

This Guide combines the concepts of existing GMP principles from the WHO (World Health Organization) GMP guidelines for excipients, the IPEC Good Manufacturing Practices Guide for Bulk Pharmaceutical Excipients 2001, IQA PQG PS 9100:2002 Pharmaceutical Excipients and international quality management system requirements as developed by the International Organization for Standardization (ISO). In view of the increasing globalisation of the pharmaceutical industry and the harmonisation of pharmaceutical registration requirements, relevant portions of the manufacturing concepts detailed in these schemes are employed throughout this Guide.

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. For example these sections recommend measures to limit excipient contamination. 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.

The Appendices cover supporting guidance for excipient GMP including Auditing Considerations (which describes key criteria to be considered when auditing an excipient manufacturing facility), along with Definitions, Glossary and Bibliography.

## 2 DEFINITIONS

(SEE ALSO APPENDIX B)

## 3 GENERAL GUIDANCE

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

### 3.1 Pharmaceutical Excipients

Pharmaceutical 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 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.

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

Judgement based on risk analysis and a thorough knowledge of the process is required to determine from which processing step GMP should be implemented. 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 pharmaceutical excipients. Excipient manufacturers should identify the quality management processes required to assure excipient quality.

Where manufacturing, testing or other operations that could affect excipient quality are outsourced 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.

### 4.2.2 Quality Manual

The excipient manufacturer should prepare a quality manual describing the quality management system, the quality policy and the commitment of the excipient manufacturer to applying the appropriate GMP and quality management standards contained in this Guide. This manual should include the scope of the quality management system, reference to supporting procedures and a description of the interaction between quality management processes.

### 4.2.3 Control of Documents

The excipient manufacturer should establish and maintain procedures for the identification, collection, indexing, filing, storage, maintenance and disposition of controlled documents, including 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 may include a unique identifier, date of issue and revision number to facilitate identification of the most recent document. The department with the responsibility for issuing the documents should be identified. Where practical, changes and the reasons for the change should be documented.

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, filing, storage, 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. Pertinent subcontractor quality data should be an element of these records.

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

Records should be kept for a defined period. This period should be appropriate to the excipient, its expiry date or re-evaluation interval. 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.

### 4.3 Change Control

The excipient manufacturer should establish and maintain procedures to evaluate and approve changes that may have an impact on the quality of the excipient. For example this may include changes to:

- raw materials or packaging and their sources,
- material specifications,
- test methods,
- manufacturing and analytical equipment,
- production processes,
- manufacturing or packaging sites etc.

A function that is independent from production (such as regulatory affairs, quality assurance, etc.) should have the responsibility and authority for the final approval of changes.

Customers and, if necessary, regulatory authorities (for example for Drug Master Files (DMFs) or Certificates of Suitability to the European Pharmacopoeia (CEPs)) should be notified of significant changes from established production and process control procedures that may affect excipient quality (see also 7.2.3 and Appendix C). The IPEC-Americas *Significant Change Guide for Bulk Pharmaceutical Excipients* provides criteria that the excipient manufacturer can use to determine when to involve the pharmaceutical customer, based on the likelihood that a proposed change will impact their drug product.

## 5 MANAGEMENT RESPONSIBILITY

### 5.1 Management Commitment

Top management should demonstrate to the organisation the importance it places on customer satisfaction and compliance with the appropriate regulations and standards. This should be accomplished through the development of a quality policy and establishment of quality objectives. Progress towards the documented quality objectives should be reviewed at planned intervals.

### 5.2 Customer Focus

It is the responsibility of top management to ensure that customer requirements are determined and met.

The excipient manufacturer should permit the customer or their representative to conduct audits to review its quality management system, manufacturing processes, buildings and facilities.

## 5.3 Quality Policy

Top management should demonstrate its commitment to the corporate quality policy and ensure that it is 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 objectives for adherence to GMP to ensure that the excipient manufacturer maintains and improves its performance. Objectives should be deployed throughout the organisation 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 organisation.

It should be the responsibility of a unit independent of production, such as the quality unit, to:

- ensure quality-critical activities are undertaken as defined,
- approve suppliers of quality-critical materials and services,
- approve or reject raw materials, packaging components, intermediates and finished excipients,
- ensure that there is a review of production records to ensure that no errors have occurred or, if errors occur, that they are fully investigated,
- participate in reviewing and authorising changes to processes, specifications, procedures and test methods that potentially affect quality (see also 4.3) and in investigating 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 a self inspection programme of the quality management system.

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.

An organisation 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 organisation. The communication should also provide information about the effectiveness of the quality management system.

Top management should be notified in a timely manner 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 organisation'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.

#### 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 preventive actions,
- changes that could affect the quality management system.

#### 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

There should be sufficient 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.

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. 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. Qualified individuals should conduct GMP training with sufficient frequency to ensure that employees remain familiar with applicable GMP principles. 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 program 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 protective apparel such as head, face, hand and arm coverings should be worn as appropriate to the duties performed. Jewellery and other loose items, including those in pockets, should be removed or covered. Only authorised personnel should enter those areas of the buildings and facilities designated as limited access areas.

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 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).

### 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 etc.) 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.

There should be adequate facilities for the 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).

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

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 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 such activities 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 suitable back-up or archival systems such as copies of the program and files,
- assurance that changes are verified and documented and only made by authorised personnel.

### 6.3.3 Utilities

Utilities (for example nitrogen, compressed air, steam etc.) 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 assure 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.

## 6.4 Work Environment

Where the excipient is exposed during manufacture it should be in an appropriate environment to minimise contamination. The manufacturer should apply suitable controls to maintain that environment.

### 6.4.1 Air Handling

Where an air handling system is installed to provide protection to the excipient, the excipient manufacturer should demonstrate its effectiveness.

Excipient production unit air handling systems should be designed to prevent 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.

Special environments required by some processes should be monitored to assure 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 in the special 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 following purification of the excipient.

### 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.

Waste should be segregated and disposed of in a timely and appropriate manner. If waste is not disposed of immediately, it should be suitably identified.

### 6.4.4 Pest Control

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

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.

### 6.4.6 Drainage

In areas where the excipient is open to the environment, 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.

#### 6.4.7 Washing and Toilet Facilities

Adequate personal washing facilities should be provided, including hot and cold water, soap or detergent, air dryers or single service towels and clean toilet facilities easily accessible to working areas. Adequate facilities for showering and/or changing clothes should be provided, where appropriate.

## 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 programs for quality-critical materials including 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,
- environmental and hygiene control programs to minimise contamination.

### 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 (for example pharmacopoeia material and general monographs), should be agreed by both parties. Requirements not stated by the customer but necessary for specified or intended use, where known, should be considered.

#### 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 provision for providing accurate and pertinent communication to the customer. Master copies of documents such as specifications and technical reports should be controlled documents. Provision should be made for replying to customer enquiries, contracts and order handling requirements. Customer feedback and complaints should be documented. Customers should be notified of significant changes (see also 4.3). For additional change notification information refer to IPEC-Americas *Significant Change Guide for Bulk 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. Full GMP is not always applicable 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

Excipient manufacturers should have a system for selecting and approving suppliers of quality-critical materials and services (for example subcontract manufacturers and laboratories). Supplier approval by the quality unit should require an 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, style, 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 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 acceptance. 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 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 assure 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 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,
- 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, deviation and their investigations,
- results of final product inspection.

#### 7.5.1.2 Equipment Cleaning

The manufacturer should design and justify cleaning and sanitisation procedures and provide evidence of their effectiveness. 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. There should be a record confirming that these procedures have been followed.

Equipment and utensils should be cleaned and sanitised where critical to excipient quality and at appropriate intervals to prevent contamination and cross-contamination of the excipient. The cleaning status of equipment should be recorded appropriately.

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.

For continuous processing the frequency of equipment cleaning should be determined by the manufacturer and justified.

#### 7.5.1.3 Recovery of Solvents, Mother Liquors and Second Crop Crystallisations

Where solvents are recovered and reused in the same process or different processes they should meet appropriate standards prior to reuse or mixing with other approved material.

Mother liquors or filtrates containing recoverable amounts of excipient, reactants or intermediates are frequently reused. Such processes should be documented in the production records or logs to enable traceability.

#### 7.5.1.4 In-process Blending or Mixing

In process blending or mixing to assure 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 assure homogenous mixing of materials to the extent feasible and should be reproducible from batch to batch.

#### 7.5.1.5 In-process Control

In-process inspection and testing should be performed based upon monitoring the process or actual sample analysis at defined locations and times. Sampling methods should be documented to ensure that the sample is representative and clearly labelled.

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

The results of in-process tests should be recorded and should conform to 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. There should be 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 assure 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 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.

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

#### 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

An important factor in the assurance of product quality includes the adequate design and control of the manufacturing process because product testing alone is not sufficient to reveal variations that may have occurred. Each step of the manufacturing process should be controlled to the extent necessary to ensure that the excipient meets established specifications.

The concept of process validation is a key element in ensuring that these quality assurance goals are met. The process reactions, operating parameters, purification steps,

impurities and key tests needed for process control should be documented, thus providing the basis for validation.

The full validation program that is typically performed in the pharmaceutical industry may not always be carried out by the excipient manufacturer. However, the excipient manufacturer should demonstrate the consistent operation of each manufacturing process, for example through process capability studies, development and scale-up reports etc.

### 7.5.3 Identification and Traceability

#### 7.5.3.1 Traceability

Quality-critical items, for example raw materials, packaging materials, intermediates and finished excipients 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,
- 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 so that their identity, quality and purity are not affected. 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.

#### 7.5.5.2 Packaging Systems

An excipient packaging system should include the following features:

- documented specifications and examination or testing methods,
- cleaning procedures where containers are reused,
- tamper-evident seals,
- 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 re-used, previous labelling should be removed or defaced. If the containers are repetitively used solely for the same excipient, previous batch numbers or the entire label should be removed or completely obliterated.

#### 7.5.5.3 Delivery and Distribution

Identification and traceability of quality-critical aspects are required of excipient manufacturers. Distribution records of excipient shipments should be kept. These records should identify, 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. Excipients should only be supplied within their expiry and/or retest period.

## 7.6 Control of Measuring and Monitoring Devices

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

calibration of instruments and equipment at suitable intervals in accordance with an established documented program. This program should contain specific directions, 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 calibration. The current calibration status of quality-critical equipment should be known and verifiable to users.

# 8 MEASUREMENT, ANALYSIS AND IMPROVEMENT

## 8.1 General

The organisation 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 organisation 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 that strive 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 activities comply with planned arrangements and the effectiveness of the quality management system. Audits should be scheduled on the basis of the status and importance of the activity. Audits and follow-up actions should be carried out in accordance with documented procedures.

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.

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

### 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 the test methods and procedures to ensure the product consistently meets specifications.

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

#### 8.2.4.1 Laboratory Controls

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 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.

There should be a documented procedure for the preparation of laboratory reagents and solutions. Purchased reagents and solutions should be labelled with the proper name, concentration and expiry date. Records should be maintained for the preparation of solutions including the name of the solution, 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 documented procedure.

Retest sample results may only be used to replace the original test result if it is demonstrated that the original result is erroneous based on a documented investigation.

When statistical analysis is used both the original and retest data must be included. The OOS procedure should define which statistical techniques are to be used and under what circumstances.

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

Where practical, a representative sample of each batch of the excipient should be retained. The retention period should be appropriate to the expiry or re-evaluation date. The retained samples should be stored and maintained in such a manner that they are readily retrievable in facilities that provide a suitable environment. The sample size should be at least twice the amount required to perform complete specification testing.

#### 8.2.4.5 Certificates of Analysis

The organisation 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-Americas *Certificate of Analysis Guide for Bulk Pharmaceutical Excipients* and the *UK Guidance on Certificates of Analysis* from *The Rules and Guidance for Pharmaceutical Manufacturers and Distributors*.

#### 8.2.4.6 Impurities

Where possible, excipient manufacturers should identify and set appropriate limits for impurities. The 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.

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.

#### 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.

Where historical data do not exist a documented testing and/or evaluation program designed to assess the stability characteristics of the excipient should be undertaken. The results of such stability testing and/or evaluation should be used in determining appropriate storage conditions and retest or expiry dates. The testing program should include the following:

- the number of batches, sample sizes and test intervals,
- storage conditions for samples retained for testing,
- suitable stability-indicating test methods,
- storage of the excipient in containers that simulate the market container, where possible.

The stability of excipients may be affected by undetected changes in raw materials or subtle changes in manufacturing procedures or storage conditions. Excipients may also be shipped in a variety of packaging types that can affect their stability (for example plastic or glass bottles, metal or plastic drums, bags, tank cars or other bulk containers, etc.).

Some excipients may be available in different grades (for example various molecular weights of a polymer or different monomer ratios, different particle sizes, bulk densities etc.) or may be mixtures of other excipients. These excipients may be very similar to others within a product group. Minor quantitative differences of some of the components may be the only significant variation from one product to another. For these types of excipients, a “model product” approach may be appropriate to assess the stability of similar excipients. Stability studies of this type should involve selection of several “model products” that would be expected to simulate the stability of the product group being assessed. This selection should be scientifically sound and documented. Data from stability studies of these “model products” can be used to determine theoretical stability for similar products.

#### 8.2.4.8 Expiry/Retest Periods

An expiry or retest period should be assigned to each excipient and communicated to the customer. Common practice is to use a retest period, rather than an expiry period.

### 8.3 Control of Nonconforming Product

Raw material, intermediate or finished excipient found not to meet its specification should be clearly identified and controlled to prevent inadvertent use or release for sale. A record of nonconforming product should be maintained. Incidences of non-conformance should be investigated to identify the cause. The investigation should be documented and action taken to prevent recurrence.

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

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.

### 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 documented that the excipient may be made in that manner. In all other cases, the guidance for reworking should be followed.

### 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.

When the need to rework an excipient is identified an investigation and evaluation of the cause is required.

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.

Batches of excipients that do not conform to specifications individually must not be blended with other batches that do conform in an attempt to hide adulterated or sub-standard material.

### 8.3.3 Returned Excipients

Returned excipients should be identified and quarantined until the quality unit has completed an evaluation of their quality. There should be procedures for holding, testing reprocessing or reworking of the returned excipient. 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.

## 8.4 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:

- causes of nonconforming product,
- 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,
- 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 to deal with problems at a level corresponding to the risks,
- implementing and recording changes in procedures resulting from preventive action.

# APPENDIX A AUDITING CONSIDERATIONS

## A1. Introduction

Many excipients are used in food, cosmetic or industrial products as well as in pharmaceuticals. Thus 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 manufacturer's quality management system.

For additional information on auditing refer to the IPEC-Americas *Good Manufacturing Practices Audit Guideline for Bulk Pharmaceutical Excipients*. Also for guidance on the auditing process refer to the IQA 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.

Changes in excipient manufacturing processes may result in changed physical or chemical properties of the excipient that are only evident during subsequent processing or in the finished dosage form. This is particularly important in the context of the pharmaceutical product approval process where bioequivalence comparisons are made between pivotal, clinical trial batch ("bio batch") production and commercial scale-up batches. Changes made to the excipient supplied for the commercial product from the excipient supplied for the bio batch should be such that they do not impact the quality and performance of the commercial drug product. Scale-up of excipients to commercial production may involve several stages and data may be required to demonstrate consistency between batches through the scale-up process.

### 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 assuring 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 engineers, laboratory analysts, purchasing agents, computer experts, maintenance or other appropriate personnel as appropriate to the scope and purpose of the audit. External auditors must respect confidentiality of the manufacturer’s processes and other disclosures.

An audit should focus on the quality-critical processing steps that are necessary to produce an excipient that meets the established physical and chemical 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:

- 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 non-conformance, 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 Material Review Board 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.

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

Documentation required for the early steps in the process need not be as comprehensive as in the latter stages of the process. It is important that a chain of documentation exists and that this is complete when:

- the excipient can be identified and quantified for those processes where the molecule is produced during the course of the process. For batch production a theoretical mass balance may also be established with appropriate limits, as deviations from tolerance are a good indicator of a loss of control,
- an impurity or other substance likely to adversely affect the impurity profile or form of the molecule is identified and subsequent attempts are made to remove it.

As chemical-processing proceeds, a chain of documentation should be established 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.

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.

Complete documentation should be continued throughout the remainder of the process for quality-critical processing steps until the excipient is packaged and delivered to the end user. The batch should be homogenous within the manufacturer's specifications. This does not necessitate the final blending of continuous process material if process controls can demonstrate compliance to specifications throughout the batch.

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,
- adequate stability data to support the intended period of use of the excipient. These data can be obtained from historical data, actual studies on the specific excipient or from applicable "model product" studies that can reasonably be expected to simulate the performance of the specific excipient.

## APPENDIX B DEFINITIONS AND GLOSSARY

As used throughout this Guide, the terms below have the following meaning. Wherever possible definitions used by the International Conference on Harmonisation have been used as the basis for this glossary.

**Acceptance criteria**
Numerical limits, ranges or other suitable measures of acceptance for test results.

**Active Pharmaceutical Ingredient (API)**
Any substance or mixture of substances, intended to be used in the manufacture of a drug product and that, when used in the production of a drug, becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease or to affect the structure or any function of the body of man or animals.

**Adulterated Material**
A material that has been contaminated with either a foreign material or not manufactured using GMP. This does not pertain to a material that simply does not meet physical or chemical specifications.

**Batch (Lot)**
A specific quantity of material produced in a process or series of processes so that it can be expected to be homogeneous. In the case of continuous processes, a batch may correspond to a defined fraction of the production. The batch size can be defined either by a fixed quantity or by the amount produced in a fixed time interval.

**Batch Number (Lot Number)**
A unique combination of numbers, letters and/or symbols that identifies a batch and from which the production and distribution history can be determined.

**Batch Process**
A process that produces the excipient from a discrete supply of raw materials that are present before the completion of the reaction.

**Batch Record**
Documentation that provides a history of the manufacture of a batch of excipient.

**Calibration**
The demonstration that a particular instrument or measuring device produces results within specified limits by comparison with those produced by a reference or traceable standard, over an appropriate range of measurements.

**CEP (Certificate of Suitability to the European Pharmacopoeia)**
Certification granted to individual manufacturers by the European Directorate for the Quality of Medicines (EDQM) when a specific excipient or active ingredient is judged to be in conformity with a Ph. Eur. monograph.

**Certificate of Analysis**
A document listing the test methods, specification and results of testing a representative sample from the batch to be delivered.

**Commissioning**
The introduction of equipment for use in a controlled manner.

**Contamination**
The undesired introduction of impurities of a chemical or microbiological nature or foreign matter into or onto a raw material, intermediate or excipient during production, sampling, packaging or repackaging, storage or transport.

**Continuous Process**
A process that continually produces material from a continuing supply of raw material.

**Critical**
A process step, process condition, test requirement or other relevant parameter or item that must be controlled within predetermined criteria to ensure that the excipient meets its specification.

**Cross-Contamination**
Contamination of a material or product with another material or product.

**Customer**
The organisation receiving the excipient once it has left the control of the excipient manufacturer; includes brokers, agents and users.

**Deviation**
Departure from an approved instruction or established standard.

**Drug Master File (DMF)**
Detailed information about the manufacture of an excipient that is submitted to the United States Food and Drug Administration.

**Drug (Medicinal) Product**
The dosage form in the final immediate packaging intended for marketing.

**Excipient**
Substances other than the API which have been appropriately evaluated for safety and are intentionally included in a drug delivery system.

**Expiry (Expiration) Date**
The date designating the time during which the excipient is expected to remain within specifications and after which it should not be used.

**Impurity**
A component of an excipient that is not intended to be present but arises as a consequence of the manufacturing process.

**In-process Control/Testing**
Checks performed during production to monitor and, if appropriate, to adjust the process and/or to ensure that the intermediate or excipient conforms to its specification.

**Intermediate**
Material that must undergo further manufacturing steps before it becomes an excipient.

**Lot**
See Batch.

**Manufacture/Manufacturing Process**
All operations of receipt of materials, production, packaging, repackaging, labelling, relabelling, quality control, release and storage of excipients and related controls.

**Master Production Instruction (Master Production and Control Record)**
Documentation that describes the manufacture of the excipient from raw material to completion.

**Material**
A general term used to denote raw materials (starting materials, reagents and solvents), process aids, intermediates, excipients, packaging and labelling materials.

**Model Product**
A product that represents a group of similar products with respect to composition, functionality or specification.

**Mother Liquor**
The residual liquid that remains after crystallisation or isolation processes.

**Packaging Material**
A material intended to protect an intermediate or excipient during storage and transport.

**Production**
Operations involved in the preparation of an excipient from receipt of materials through processing and packaging of the excipient.

**Quality Assurance**
The sum total of the organised arrangements made with the object of ensuring all excipients are of the quality required for their intended use and that quality systems are maintained.

**Quality Control**
Checking or testing that specifications are met.

**Quality-critical**
Describes a material, process step or process condition, test requirement or any other relevant parameter that directly influences the quality attributes of the excipient and which must be controlled within predetermined criteria.

**Quarantine**
The status of materials isolated physically or by other effective means pending, a decision on their subsequent approval or rejection.

**Raw Material**
A general term used to denote starting materials, reagents and solvents intended for use in the production of intermediates or excipients.

**Record**
Document stating results achieved and/or providing evidence of activities performed. The medium may be paper, magnetic, electronic or optical, photographic etc. or a combination thereof.

**Re-evaluation Date (Retest Date)**
The date when the material should be re-examined to ensure that it is still in conformance with the specification.

**Reprocessing**
Repetition of an activity that is a normal part of the manufacturing process and that has been documented previously.

**Retrieval**
Process for the removal of an excipient from the distribution chain.

**Reworking**
Subjecting previously processed material that did not conform to standards or specifications to processing steps that differ from the normal process.

**Specification**
A list of tests, references to analytical procedures and appropriate acceptance criteria that are numerical limits, ranges or other criteria for the tests described for a material.

**Stability**
Continued conformance of the excipient to its specifications.

**Top Management**
Person or group of people who direct and control an organisation at the highest level. The highest level can either be at the site or corporate level and will depend on the way that the quality management system is organised.

**Traceability**
Ability to determine the history, application or location that is under consideration, for example origin of materials and parts, processing history or distribution of the product after delivery.

**Validation**
A documented program that provides a high degree of assurance that a specific process, method or system will consistently produce a result meeting predetermined acceptance criteria.

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